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PTERYGOID PLEXUS VENOGRAPHY

by

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While evaluating the usefulness of intra-osseous venography in determining the presence of neoplastic intramedullary invasion of the lower jaw it became evident that certain hitherto radiologically hidden venous pathways of the pterygoid fossa could be rendered visible. In other words, the injection of contrast medium into the posterior portion of the mandible does not only outline the medullary cavity of the mandible but also allow the demonstration of the pterygoid venous plexus and of some of its tributaries.

Technique. Under local anesthesia, a 16 or 18 gauge Rosenthal bone marrow aspiration needle is introduced into the medullary cavity of the mandible. The needle is best advanced with a rotary motion through the inferior edge of the mandible so as to secure its position in the vertical axis of the lower jaw. Sometimes considerable effort is required to penetrate the rather compact cortex of the posterior third of the mandible. We prefer the inferior approach since it allows more adequate positioning of the needle within the medullary cavity. The lateral approach is technically easier, but does have the disadvantage that the needle readily pierces through the entire thickness of the jaw, because of the dumbbell-shaped cross section of the mandible, and may cause extravasation of the contrast medium.

Adequate anesthesia of the inferior dental nerve is readily obtained by injecting 1 ml of a 1 % solution of Procaine hydrochloride directly into the medullary canal, after the correct positioning of the needle has been verified by aspiration of bone marrow.

The head of the sitting patient is then placed in a lateral position on the Schönander head unit, with the mandible to be injected near the film. The table is in the straight vertical plane and the head of the patient is slightly tilted (approximately 10°) so as to have the temporo-parietal region in contact with the table, while the mandible remains free. This allows easy access to the needle without disturbing the position of the patient. The roentgen tube must be inclined downwards (approximately 20°) in order to adequately demonstrate the pterygoid area.

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Fig. 1.

Fig. 2.

Fig. 1. Roentgenogram taken after injection of 2 ml of contrast medium. 1 = veins in medullary canal of mandible; 2 = facial vein and branches; 3 = lower portion of retromandibular vein.

Fig. 2. Roentgenogram taken after introduction of 4 ml of contrast substance. Gradually increasing filling of medullary cavity, and of the main veins involved in its drainage. 4 = trunk of superior thyroid vein; 5 = alveolar foramen; 6 = alveolar vein; 7 = portion of internal maxillary vein.

It is preferable to connect the needle to an ordinary 10 ml manual syringe by means of a piece of plastic tubing. Usually, 5 to 8 ml of contrast substance are injected under constant and moderate pressure. We prefer to use a 50 per cent solution of Hypaque (sodium 3, 5 diacetamido — 2, 4, 6 triiodobenzoate). (Hypaque was made available through the courtesy of Winthrop Laboratories, Inc., New York.) In our experience, one film to verify the correct positioning of the patient, and one film taken during the injection of the last 1 or 2 ml of contrast medium have been found to be entirely sufficient.

Discussion

As demonstrated in the accompanying roentgenograms, moderate filling of the medullary cavity is obtained. The contrast substance is drained through several small submental veins, as well as through branches of the facial vein and the alveolar vein. Most of the contrast medium, however, fills a conglomerate of veins located posteriorly along the superior aspect of the ascending ramus of the mandible, as well as between condyle and coronoid process. This network of veins corresponds to what is usually known as pterygoid venous plexus.

This latter plexus covers the inner surface of the internal pterygoid muscle and surrounds the external pterygoid muscle. It receives branches

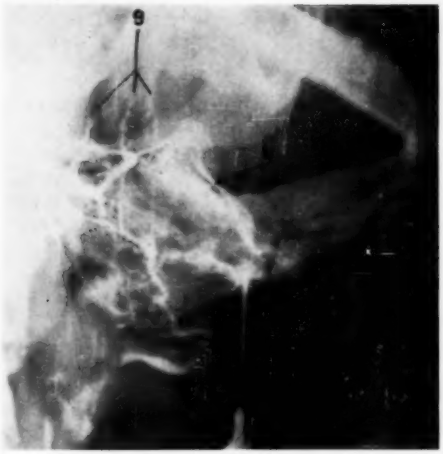

Fig. 3. Roentgenogram taken during injection of the last 1 or 2 ml of contrast medium. Total amount of Hypaque was 8 ml. Good visualization of venous network along ascending ramus of mandible and in pterygoid fossa. 8 = bucinator vein, which connects the pterygoid plexus (9) with the facial vein.

which correspond with and accompany the branches of the internal maxillary artery, *i. e.* vidian, pterygopalatine, sphenopalatine, infra-orbital, posterior superior dental, posterior palatine, buccal, deep temporal, pterygoid, masseteric and inferior dental veins, and the vena comites of the middle meningeal artery. The pterygoid plexus is a tributary of the internal maxillary vein, and communicates freely with the facial vein, and with the cavernous sinus by branches through the foramen ovale, foramen lacerum medium and foramen Vesalii.

Conclusions

It is certainly of interest from the anatomo-radiologic standpoint to note that intra-osseous venography of the posterior third of the mandible renders possible the visualization of the pterygoid plexus. This venous network is hidden in an anatomically rather complex area and surgically practically never exposed in detail. Yet, by virtue of its numerous tributaries, and various intra-cranial communications, this plexus must be considered as an important link in the chain of cranio-facial venous pathways.

Although speculations of clinical nature are outside the scope of this presentation it is nevertheless well possible that the radiologic demonstration of the pterygoid plexus may prove to be of value in presence of certain morbid processes affecting the head and neck area.

SUMMARY

The radiologic demonstration of certain venous pathways of the pterygoid area is presented and documented by a series of roentgenograms. The vascular anatomy of this particular region is elaborated upon. Visualization of the pterygoid venous plexus, and of some of its branches, has been obtained by injecting contrast medium directly into the medullary cavity of the mandible. The technique of injection, as well as the positioning of the patient are described.

ZUSAMMENFASSUNG

Die radiologische Darstellung gewisser venöser Verläufe im Pterygoideusgebiet wird vorgelegt und durch eine Reihe von Röntgenbildern dokumentiert. Die Gefässanatomie dieses speziellen Gebietes wird sorgfältig ausgearbeitet. Durch Injektion des Kontrastmittels direkt in das Knochenmark des Unterkiefers ist es gelungen, den venösen Plexus pterygoideus und einige seiner Äste sichtbar zu machen. Die Injektionstechnik sowie die Lagerung des Patienten werden beschrieben.

RÉSUMÉ

Présentation et illustration au moyen d'une série de radiographies de la mise en évidence radiologique de certaines voies veineuses de la région ptérygoïdienne. L'anatomie vasculaire de cette région est mise au point. La visualisation du plexus veineux ptérygoïdien et de certaines de ses branches a été obtenue par l'injection du moyen de contraste directement dans la cavité médullaire de la mandibule. La technique d'injection et la mise en place du malade sont décrites.

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THE NORMAL MOTILITY OF THE LUMBOSACRAL SPINE

by

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Roentgen examination of spinal motility has been performed at the Roentgen Department of the Neurologic Clinic, Prague, since 1951. By routine dynamic roentgen examination of the lumbosacral spine we have been able to determine different signs of disturbances of spinal motility. Our knowledge of spinal dynamics under normal conditions being, however, imperfect, we have also carried out corresponding roentgen examinations in healthy subjects.

In order to determine the dynamics of the lumbosacral spine under normal conditions in healthy subjects a group of 100 individuals were investigated. This material consisted of those who had never had radicular pain or lumbago, and, as far as was known, no previous spinal injuries. As it is always difficult to find a sufficient number of such healthy individuals among the older subjects, only those in the 15 to 25 year age group were considered. Approximately one half were under 20 and the other over 20 years of age.

The lumbosacral spine of the subjects was examined in the erect lateral position in extreme anteflexion and retroflexion. The tube distance was 1.20 m.

Of the 100 cases 77 had roentgenologic findings which seem to represent the normal spinal dynamics. The spine formed in anteflexion as well as in retroflexion a regular uninterrupted arch, in which no vertebra deviated from a continuous line; a line drawn through the posterior margins of the vertebral bodies was therefore continuous. The intervertebral spaces in anteflexion showed regular and proportional anterior narrowing and posterior widening, whereas in retroflexion regular and proportional anterior widening and posterior narrowing occurred (Figs. 1 and 2).

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Fig. 1. Normal lumbar spine in anteflexion.

Fig. 2. Normal lumbar spine in retroflexion.

There are also 12 cases with a transitional lumbosacral vertebra, higher anteriorly than posteriorly, in the material. These cases had slight alterations of spinal mobility associated with such a vertebra. The following changes were observed: 1) Slight diminution of spinal mobility in anteflexion in the region of L4—S1 (Fig. 3). 2) Slight forward displacement of the fourth upon the fifth lumbar vertebra (Fig. 4). 3) Normal mobility in retroflexion always present.

The diminution of mobility in L4—S1 in anteflexion is without doubt caused by the shape of the fifth lumbar vertebra. The higher anterior part of the vertebra acts as a natural obstacle to normal expansion of mobility. The slight forward displacement of the fourth lumbar vertebra may be said to be a sign of a minor degree of compensatory hypermotility,

Fig. 3. Decrease of motility in the L4—S1 segment.

Fig. 4. Hypermotility in the L4—5 segment.

allowing for the diminution of the mobility in the L5—S1 segment. This anatomic anomaly has no mechanic influence in retroflexion which is therefore normal.

Of these 12 cases, 2 were 15 and one 17 years old, the age of the subject perhaps accounting for the slight vertebral displacements.

In our opinion the spinal dynamics of these 12 cases are also to be considered as normal. The dynamic irregularities due to the normal anatomic anomaly of the transitional lumbosacral vertebra may be supposed to be a normal dynamic variation.

Thus in the whole of our group of 100 individuals normal spinal dynamics were found in 89 cases, *i. e.* in 89 per cent.

Of the remaining 11 cases 3 had disturbances of the spinal motility to a minor degree and 4 had more marked dynamic deviations which, in our opinion, were not associated with normal conditions. Moreover the remaining 4 cases had definitely abnormal dynamic findings. One case had a slight forward displacement of the fourth upon the fifth lumbar vertebra, constant in all positions, due to spondylolysis of the former vertebra. The second case had spondylolisthesis of L5 with a constant

forward displacement of L5 upon S1. In the third case there was a large intraspongial herniation in the lower terminal plate of L4 with degeneration of the disc and hypermotility of the L4—5 joint. The fourth case showed a dynamic block of L4—L5 and slight forward displacement of the fifth lumbar vertebra in anteflexion. This examination was performed in 1952 in what was supposed to be a healthy individual and who was re-examined in 1955 as a subject with low back pain.

It is evident that the material is not ideal. For precise delimitation of the spinal dynamic norm an investigation of larger groups of individuals of different ages, employment, geographic conditions etc. is necessary. Nevertheless our present results seem to indicate that probably this dynamic norm exists, that it is a relatively well-defined entity, and that it is useful in evaluating the pathologic findings and in differentiation between normal and abnormal conditions.

As regards the abnormal dynamics in healthy individuals it is open to further investigation to determine whether they may be looked upon as indications of a certain predisposition to intervertebral disturbances and to manifestations of radicular syndromes. This point seems to be important from the standpoint of the prevention of symptoms.

SUMMARY

A material of 100 individuals was examined with a view of determining the dynamics of the lumbosacral spine under normal conditions. Disturbances were found to be present in 11 cases and in 4 of these were marked. The significance of the findings is discussed.

ZUSAMMENFASSUNG

Ein Material von 100 Individuen wurde in der Absicht, die Dynamik des lumbosakralen Abschnittes der Wirbelsäule unter normalen Bedingungen festzustellen, untersucht. Anomalien lagen in 11 Fällen vor und in 4 von diesen traten sie deutlich hervor. Die Bedeutung der Befunde wird besprochen.

RÉSUMÉ

Une série de 100 sujets a été examinée pour préciser la dynamique du rachis lombosacré dans des conditions normales. L'auteur a trouvé des troubles de la dynamique dans 11 cas, marqués dans 4 des cas. Il étudie l'intérêt de ces constatations.

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NEWER CONTRAST MEDIA FOR USE IN CHOLEGRAPHY

by

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Cholegraphy, or intravenous cholecystocholangiography, represents one of the most significant recent advances in the field of roentgen studies of the biliary tract and, judging from the experiences reported in the European and American literature, the usefulness, dependability, and safety of the procedure are now well established and widely accepted.

Telepaque (17), with a three-iodinated molecule, introduced in 1949, resulted in improved gallbladder filling and, for the first time, in consistently good outlining of the major portion of the bile ducts. Thus the era of oral cholangiography was introduced (18, 29) and the appearances of the normal bile ducts in the intact human subject were established. The caliber of the normal hepatic and common bile ducts was determined at 0.5 to 0.6 cm, and of the cystic duct at 0.2 to 0.3 cm. The importance of deviations from these measurements, and especially the presence of dilatation, as evidence of disease, became obvious and was readily proved (18).

The oral method enables us to study the anatomy and physiology of the gallbladder and of the ducts along the outflow path — the cystic and common bile duct. The hepatic ducts, the bile ducts in patients with no gallbladder filling, and the bile ducts in the cholecystectomized patients could not be adequately and consistently shown. Cholegraphy filled this gap and made possible a complete roentgen study of the biliary tract.

In 1952, sodium iodipamide, a compound with a six-iodinated molecule was introduced in Europe as Biligrafin 20 % (Schering A. G., Berlin) and in North America as Cholografin 20 % (E. R. Squibb, New York).

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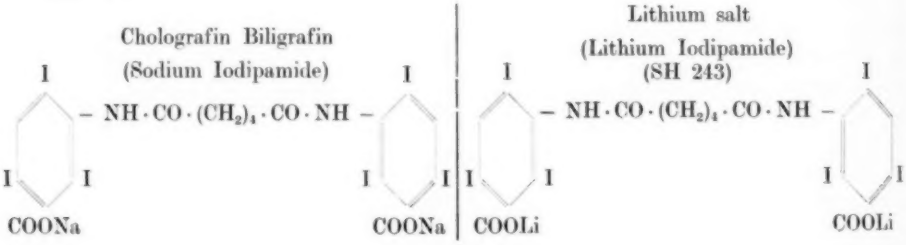
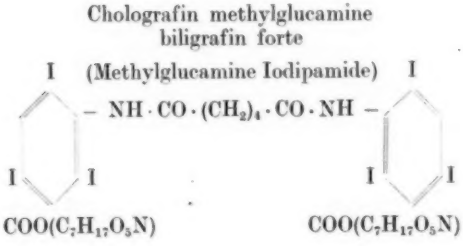
Because of its high iodine content it presented a convenient and reliable medium for rapid outlining of the biliary tract irrespective of whether or not the gallbladder was present and independent of the ability of the latter to concentrate its contents.

With the use of Cholografin the major intra- and extra-hepatic ducts are well outlined in the cholecystectomized patient. Not infrequently the gallbladder has been filled with Cholografin after failure with Telepaque in the apparently normal state as well as in disease. On the other hand the ability of the gallbladder to concentrate its contents cannot be determined by this method because of the rapid transit of the gallbladder contents by virtue of the nature and procedure of the examination. Further limitations to this method are obstructive jaundice, and severe liver and kidney disease. The first two are also contra-indications to the use of Telepaque and other orally administered contrast media.

In a continued effort to improve further the contrast medium, Schering A. G. have replaced the sodium iodipamide with the lithium salt (1953). Its advantage was greater ease of administration through smaller total dosage. On the other hand, the toxicity was greater and the incidence and intensity of side-reactions higher. The third and best of the series appears to be Cholografin Methylglucamine (Biligrafin Forte). Its chief advantage over both of its predecessors lies in its remarkably low toxicity, with a minimum of side-reactions and a markedly increased solubility. The three preparations mentioned have the following chemical formulae:





The solubility of the lithium salt is limited to a maximum of 40 %. The methylglucamine compound is almost twice as soluble. For the purpose of ordinary cholegraphy a 52 % solution is used, while for other procedures, including hysterosalpingography, solutions up to 70 % are employed (24, 25).

Table 1

Comparison of side-reactions in 300 patients after injection of 40 ml Cholografin (Biligrafin) 20 %, 50 patients after injection of 20 ml lithium salt 40 % and 200 patients after injection of 20 ml Cholografin Methylglucamine (Biligrafin Forte) 52 %.

	Cholografin Biligrafin (Sodium iodipamide) 20 % 300 patients		Lithium salt (lithium iodipamide) 40 % 50 patients		Cholografin Methylglucamine Bibligrafin Forte (methylglucamine iodipamine) 52 % 200 patients	
	No. of patients	%	No. of patients	%	No. of patients	%
Nausea	16	5.3	5	10.0	6	3.0
Vomiting	4	1.3	3	6.0	1	0.5
Sensation of heat	7	2.3	2	4.0	5	2.5
Flushing	9	3.0	1	2.0	2	1.0
Sensation of fainting	—	—	—	—	2	1.0
Itching	1	0.3	1	2.0	—	—
Headache	1	0.3	—	—	—	—
Pain at site during injection	4	1.3	8	16.0	—	—
Chills	2	0.6	—	—	—	—
Temperature	1	0.3	—	—	—	—
Allergic reaction with marked drop in blood pressure	1	0.3	1	2.0	—	—
Diplopia (lasting 4 days)	—	—	1	2.0	—	—
Total side-reactions	46	15.3	22	44.0	16	8.0

In only a limited number of cases has it been possible to examine the same patient with all three media, or even with two media. The higher degree of toxicity of the lithium salt, evidenced by an increase in the incidence and intensity of side-reactions, was striking (Table 1). By comparison, the markedly low toxicity of the methylglucamine salt and the negligible incidence of side-reactions were remarkable. While side-reactions of varying intensity were experienced when the sodium salt was employed, practically none were encountered when the methylglucamine salt was exhibited. Furthermore, in some cases where Cholografin was used, visualization was rated as poor to fair, while biliary tract filling was appreciably improved with Cholografin Methylglucamine, and was rated as good to excellent. Based on a comparative study of the several hundred patients examined separately by each of

these contrast media, biliary tract filling with Cholografin Methylglucamine is at least as good as it is with the other media, if not superior.

We have investigated several contrast media for cholegraphy prepared by firms other than Schering A. G. and E. R. Squibb. The toxicity of these products was very low and compared very favorably with the Cholografin series. On the other hand, outlining of the gallbladder and bile ducts was much inferior. The latter consideration alone was deemed adequate for rejection of these products.

Fig. 1. Thirty minutes after injection of 40 ml contrast medium of the Cholografin Biligrafin group. Cholecystectomy 6 years prior. Dilated stump of cystic duct. The hepatic and common bile ducts are within normal limits.

Recently Schering A. G. and E. R. Squibb have made a new preparation, SH 332, available for simultaneous cholegraphy and urography. It is the methylglucamine salt of Renografin 40 % and Cholografin 20 %, in aqueous solution. This is dispensed in 20 ml ampules, the optimal dose being 40 ml. Simultaneous renal and hepatic excretion follow the intravenous injection of this medium and result in prompt outlining of the urinary and biliary tracts. Examination of the urinary tract is performed in the usual manner and is completed within 20 to 30 minutes. Examination of the biliary tract is likewise completed in the usual manner with optimal bile duct opacification occurring at 30 to 60 minutes while gallbladder filling reaches its peak at about 2 to 2 ½ hours.

Our experience with this special preparation is still limited. Further studies will be necessary and a larger series will have to be evaluated before we can fully determine its practical value.

Side-reactions. Not unlike other intravenously administered contrast media, the Cholografin-Biligrafin group produces a number of side-reactions which, however, are far less marked. Animal studies and observations in the human subject show a relatively low degree of toxicity. Severe side-reactions are minimal, and to the best of our knowledge, no deaths have been reported (4, 8, 20, 21, 22, 28, Table 1).

As in the case of the other intravenously administered contrast media, the use of the so-called preliminary sensitivity tests is of little or no value and is unreliable in predicting the occurrence of side-reactions (9, 10, 14, 20, 30).

A history of allergy or of an unfavorable reaction to a previous

intravenously injected contrast medium, calls for caution, but is not necessarily a contraindication. Premedication with antihistaminics (Benadryl or Chlor-trimeton) may prove adequate. All the same, suitable drugs and apparatus should be readily at hand should an emergency arise. According to experience so far gained the media used for cholegraphy, especially the methylglucamine salts, appear to be quite safe. Nevertheless vigilance should not be relaxed until we have accumulated large series of cases without incidence of death or serious consequences.

Excretion. The excretion of all three of the iodipamide (Cholografin-Biligrafin) compounds of sodium, lithium, and methylglucamine, is practically identical. Ninety per cent is excreted by the liver and ten per cent by the kidneys. With no obvious decrease of biliary tract filling, simultaneous hepatic and renal excretion occurs in 45 to 50 per cent of cases, the latter lasting 10 to 30 minutes, and initial renal excretion followed by delayed hepatic excretion in about 8 to 10 per cent of cases. Once excreted by the liver, these media are eliminated by the intestines with no definite evidence of reabsorption.

Blood pressure. There was essentially no significant alteration in the blood pressure as determined by measurements made before, during, and after completion of examinations with any of the three Cholografin compounds. Notable exceptions were two patients who went into a condition of shock, one after the intravenous injection of 40 ml of Cholografin and the other after the injection of 20 ml of the lithium salt 40 %. The first patient had withheld a past history of allergy, the second had no such history; the intradermal and intravenous sensitivity tests in both cases were negative. They responded promptly and recovered completely following the immediate administration of emergency medications and were discharged from hospital within 24 hours.

Jaundice. In the presence of obstructive jaundice, irrespective of its cause, there has been no evidence of hepatic excretion, and biliary tract filling has been consistently absent. On the other hand, in patients with hepatitis, hepatic excretion was absent at the maximum phase of the jaundice. As the jaundice subsided, faint biliary tract filling appeared and eventually became normal, hepatic function likewise returning to normal limits.

Delayed contrast filling of the bile ducts. This may occur in cases of incomplete obstruction of the common bile duct, with concomitant delayed emptying into the duodenum, due to impacted calculi, compression by tumors, or stenosis of the sphincter of Oddi. If the biliary tracts are not visible at the beginning of the examination this should not be interpreted as evidence of absence of hepatic excretion. Inspissated bile and bile pigment deposits in dilated ducts will slow down the flow and diffusion of bile with corresponding filling delayed; one or more

hours may elapse before this latter occurs — it should be recorded roentgenographically.

So-called 'layering'. Irregular mixing and slow diffusion of the contrast medium into the bile-filled gallbladder may appear as a filling defect simulating a concrement. Serial films may rule out the presence of a constant defect or calculus formation and a more uniform gallbladder filling will be obtained after a meal containing fats.

Reflux into the duodenum. The ready passage of the contrast medium from the common bile duct into the duodenum indicates patency and an apparent satisfactory functioning of the sphincter of Oddi. Reflux into the proximal part of the duodenum with filling of the duodenal bulb may, however, produce appearances simulating a small or residual gallbladder.

Conclusions

From our experiences with the iodipamide compounds of sodium, lithium and methylglucamine it would appear that Cholografin methylglucamine 52 % (Biligrafin Forte) is the preparation of choice; it possesses the following advantages:

1. Ease of administration through smaller total volume of the required dose.
2. Excellent filling of the biliary tract which is at least equal to, and at times superior to that produced by the other contrast media.
3. Minimal toxicity as evidenced by a markedly low incidence and intensity of side-reactions.

Our experience with SH 332 for simultaneous intravenous urography and cholegraphy remains limited. The immediate impression, however, is gained that the indications for the routine use of this preparation are likely to be few.

The conventional procedures used for testing the sensitivity of patients to the media used for cholegraphy are unreliable in predicting the occurrence of side-reactions. Considerable importance should be attached to the inviolate rule of always being in a position to institute emergency measures where necessary and of constant watchfulness over any change in the condition of the patient.

SUMMARY

The employment of the iodipamide compounds of lithium, sodium and methylglucamine in cholegraphy is reviewed. The investigation suggests that methylglucamine iodipamide (Biligrafin Forte) is the contrast medium of choice.

ZUSAMMENFASSUNG

Die Verwendung von Jodsalzverbindungen des Lithiums, Natriums und Methylglukamins bei der Cholangiographie wird kritisch gemustert. Die Untersuchung deutet darauf hin, dass das Methylglukamin-Jodsalz (Biligrafin Forte) das Kontrastmittel der Wahl ist.

RÉSUMÉ

L'auteur fait une revue des travaux sur l'utilisation en cholégraphie des composés de l'iodipamide avec le lithium, le sodium et la méthylglucamine. Ses recherches font penser que l'iodipamide méthylglucamine (Biligrafin Forte) est le contraste de choix.

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FROM THE DEPARTMENT OF RADIOLOGY, HOSPITAL OF ST. RAPHAEL, AND THE YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN, CONN., U. S. A.

A COMPARATIVE STUDY OF BROMINE AND IODINE IN CONTRAST RADIOGRAPHY

by

Robert Shapiro

In 1924, GRAHAM and COLE first introduced cholecystography. The original intravenous technique which utilized calcium tetrabromphenolphthalein was soon replaced by the sodium salt since the former had no particular advantage. In 1924 after MENEES and ROBINSON demonstrated the practicality of oral cholecystography, bromine gave way to iodine and tetraiodophenolphthalein became the drug of choice. Eventually it was in turn replaced by other organic iodine compounds *i. e.* Priodax, Teridax and Telepaque.

Because organic bromine compounds are more stable and easier to prepare than the corresponding iodine derivatives, the author decided to compare the relative merits of the two halogens in contrast radiography. This was done in the following manner:

1. Equal aliquots of Priodax and its bromine homologue (Bromidax) were prepared and radiographed at various concentrations (0.5 %, 1.0 % and 3.0 %) in a water phantom at 30 kV_p, 40 kV_p and 80 kV_p. These concentrations were selected because NEWELL demonstrated that it requires a concentration of 0.5 per cent of tetraiodophenolphthalein to visualize the average 3 cm gall bladder while the normal gall bladder concentrates tetraiodophenolphthalein in the range of 2.5 per cent.

Paradoxically enough, there was no significant difference in radio-opacity cast by the Priodax and Bromidax solutions at the lower kilovoltages. At 80 kV_p, however, the Priodax solutions were much more radio-opaque than the corresponding Bromidax solutions.

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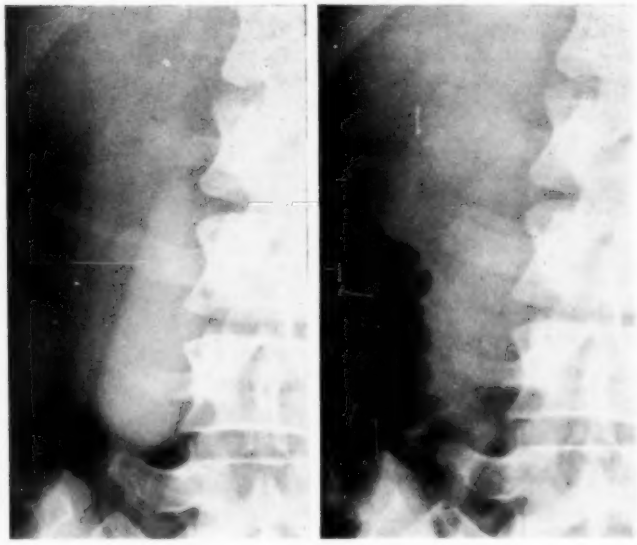

a b

Fig. 1. a) Roentgenogram of normal gall bladder 14 hours after oral ingestion of 3 g Priodax. b) Roentgenogram of gall bladder of same subject after oral ingestion of 3 g Bromidax.

2. A group of twelve normal student roentgen technicians and internes were each given 3.0 g of Priodax under basal conditions. A week later the same group took the same dose of Bromidax under identical conditions. Routine cholecystographic studies were conducted on each subject. In each case, good concentration in the gall bladder occurred with the Priodax while very poor or no concentration was observed with Bromidax (Fig. 1).

These findings are readily understandable in the light of certain physical principles. At low energy levels with more or less monochromatic radiation, the K absorption peak for bromine is greater than that for iodine. Consequently, at certain wave lengths (0.92 Å°—0.37 Å°), bromine with an atomic number of 35 is more than twice as opaque as iodine (atomic number 53) in the same percentage concentrations (Diagram 1). On the other hand, at energy levels employed for clinical radiography *i. e.* 80 kV_p, a large part of the radiation in the heterochromatic beam falls in a range where iodine absorbs a significantly greater quantity than bromine.

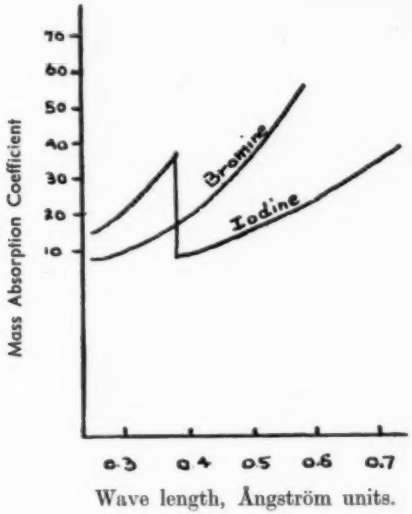

Diagram 1. Relative absorption of bromine and iodine in equal concentration by weight for various wave lengths (after NEWELL).

Conclusions. For purposes of clinical radio-opaque studies in man, iodine compounds are vastly superior to bromine compounds.

SUMMARY

A comparative study of Priodax and its bromine homologue in the laboratory and in man demonstrates varying degrees of radio-opacity at different energy levels. The physical basis of this phenomenon is presented, leading to the conclusion that iodine is superior to bromine as a radio-opaque agent in man.

ZUSAMMENFASSUNG

Vergleichende Studien mit Priodax und seiner entsprechenden Bromverbindung im Laboratorium und am Menschen zeigen bei verschiedenen Energiestufen variierende Grade von Röntgendichte. Die physikalische Unterlage für dieses Phänomen wird vorgelegt und die Schlussfolgerung gezogen, dass Jod dem Brom als röntgendichtes Agenz beim Menschen überlegen ist.

RÉSUMÉ

Une étude comparative, au laboratoire et chez l'homme, du Priodax et de son homologue bromé montre des différences de radio-opacité pour différents niveaux d'énergie. L'auteur expose la base physique de ce phénomène, qui amène à conclure que l'iode est supérieur au brome comme agent radio-opaque chez l'homme.

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SITE AS AN INFLUENCE UPON THE DENSITY OF CONTRAST MEDIA

by

Ove Mattsson

This investigation was carried out mainly to determine whether there is any relationship between the roentgenographic contrast and the position of the contrast medium in the body. The change in contrast with a variation in voltage was simultaneously studied. Three different substances, containing barium, iodine, and calcium respectively, were used, attention being focussed upon the 50 to 200 kV region.

The experimental arrangements are shown in Fig. 1. The distance between the tube (MÜLLER RÖH 5/30 — a diagnostic tube connected to a three-phase supply) and a water phantom was 290 cm, the latter consisting of a water-filled bag of thin polyethylene between stiff cardboard sheets. It was 16 cm thick. The distance between the phantom and the film was 35 cm, at which distance it was found that the influence of the secondary radiation could be ignored. The inherent filtration of the tube was 2 mm Al.

Small tubes of uniform size with an internal diameter of 10 mm, made of plastic material and containing the solutions of salts to be tested, were placed in three positions inside the phantom. One group of tubes (I) lay at the wall of the phantom nearest the tube, another (II) in the middle of the water and a third group (III) was situated at the wall nearest the film. Each group consisted of three tubes and all nine tubes were depicted simultaneously in the same film. The fairly long focus-object distance was chosen to reduce magnification. The primary screening was adjusted so that unnecessary radiation was eliminated.

In a preliminary series of experiments the concentrations of the respective substances which produced equivalent roentgenographic density were determined. These tests were made at 70 kV. The solutions

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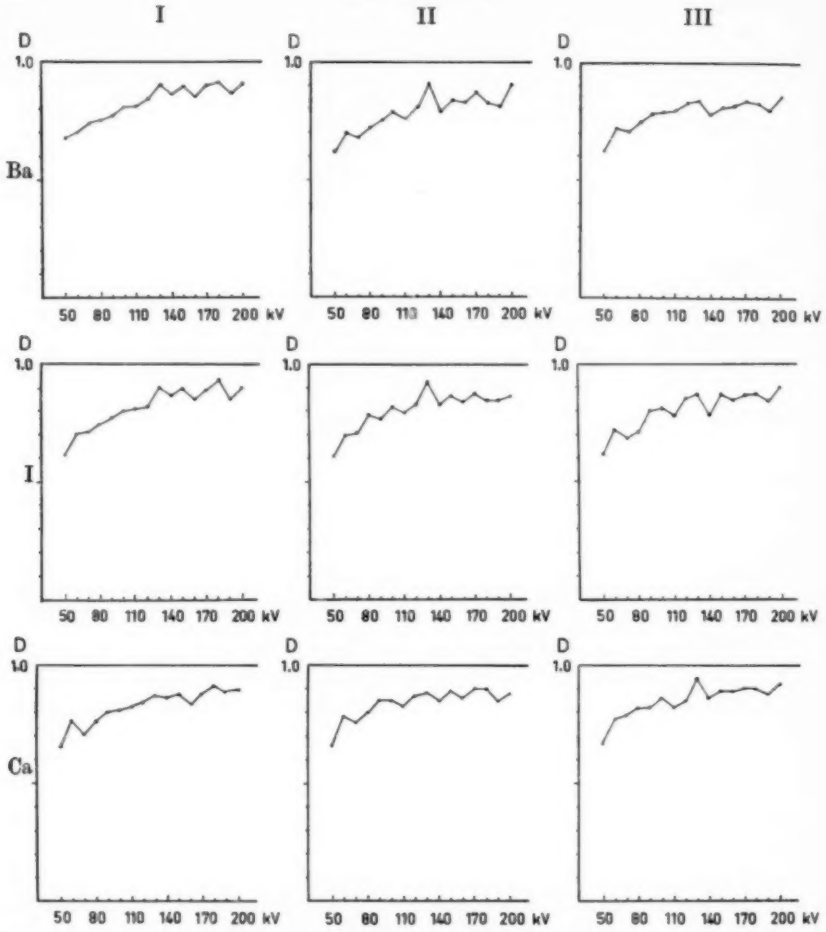

Diagrams showing densitometric readings of tube shadows with variation of voltage. The three series of graphs represent barium, iodine, and calcium, respectively. The numbers I, II, and III refer to the position of the contrast medium in the water phantom. Background density (water phantom alone) = 1.0.

of barium, iodine, and calcium, of equal density, were then distributed so that each group of test tubes I, II and III received a quantity of all three solutions. The concentrations of the solutions were quantitatively analysed with the following results:

Barium (Barium chloride solution): 5.17 g $BaCl_2 + 2H_2O$ per 100 ml.
Iodine (Potassium iodine solution): 3.82 g KI per 100 ml.
Calcium (Calcium chloride solution): 63.0 g $CaCl_2 + 6H_2O$ per 100 ml.

All films were exposed in the same casette which was fitted with Patterson Parspeed screens. The photographic processing was performed uniformly with development under constant agitation for a given time, the temperature being thermostatically controlled. The development gave a gamma value up to 3.5.

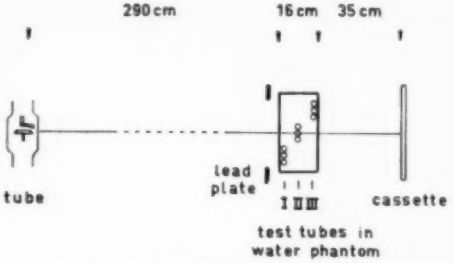

Fig. 1. Experimental arrangements, seen from above.

The experimental films were so exposed as to ensure that the background of the depicted tubes, *i. e.* the water phantom, should have a density of 1.0. Equal densities within the whole kilovoltage range were obtained with exposures calculated from curves presented earlier by the author (1956). The images of the filled tubes at 50 kV have densities between 0.6 and 0.7.

Films were exposed in 10 kV steps within the 50 to 200 kV region. The densitometric readings which were obtained are shown in the diagrams. Reference films were developed simultaneously, and from these density curves were drawn. The densitometric readings could then be translated into intensities. All values refer to a background density of exactly 1.0, and in case of diverging values adjustments have been made with help of the density curves.

The upper series of graphs are referable to the barium solution, the middle series to the iodine, and the lower to the calcium. The numbers I, II and III indicate the position within the water phantom. (Compare Fig. 1.)

In order to study the different parts of the curves and to compare them at different kilvoltage levels, the surfaces of the curves have been determined separately in successive 30 kV ranges. The results are assembled in the table. The surfaces corresponding to the complete curves of the respective substance are summarized below.

Substance and tube position

Kilovoltage	Ba			I			Ca		
	I	II	III	I	II	III	I	II	III
50—80	1,074	1,018	1,047	1,052	1,045	1,027	1,080	1,137	1,130
80—110	1,178	1,138	1,170	1,175	1,186	1,177	1,200	1,247	1,254
110—140	1,286	1,238	1,228	1,278	1,278	1,243	1,275	1,307	1,294
140—170	1,315	1,247	1,216	1,315	1,310	1,263	1,288	1,330	1,303
170—200	1,336	1,256	1,234	1,342	1,309	1,311	1,344	1,341	1,316
Total surfaces	6,189	5,893	5,895	6,162	6,128	6,021	6,187	6,362	6,297

Surfaces of curves in diagrams, measured in successive 30 kV ranges (arbitrary values).

From the results of this investigation it is obvious that the position of a contrast substance within a body has no bearing upon the roentgenographic result. The very small differences between the curve surfaces presented in the table do not exceed 5 %. The experimental errors amount to at least 5 %. (These were i. a. due to the photographic processing, measurements, and to inaccuracies in the instruments.) UHL (1954) in a study of contrast media pointed out the insignificance of the sequence of the materials passed by radiation.

The change in contrast with voltage is also shown by the graphs. There is no common dissimilarity between the shape of the curves of the different substances. With the experimental conditions similar to those obtaining in the ordinary roentgenographic technique there is no characteristic deviation apparent such as could have been caused by the absorption edges of barium and iodine, which lie at 0.331 Å and 0.373 Å respectively (COMPTON and ALLISON).

The employment of grids or a long-distance technique in diagnostic roentgenography will materially reduce secondary radiation and the conditions obtained may then be compared with the experimental arrangements described. The results may thus assume practical importance.

SUMMARY

The influence of the position of contrast media in the body on roentgenographic contrast was studied by means of a water phantom and test tubes with solutions of barium, iodine, and calcium salts. The change in contrast with voltage is also shown.

ZUSAMMENFASSUNG

Der Einfluss der Lage des Kontrastmittels in der Masse des Röntgenkontrastes wurde mit Hilfe eines Wasserphantomes und von Proberöhrchen mit Lösungen von Barium-, Jod- und Kalziumsalzen studiert. Die Veränderung des Kontrastes mit der Röhrenspannung wird auch diskutiert.

RÉSUMÉ

L'auteur a étudié l'influence sur le contraste radiographique de la situation des moyens de contraste dans le corps, grace à un fantôme d'eau et à des tubes à essai contenant des solutions de sels de baryum, d'iode, de calcium. Il examine aussi les modifications du contraste en fonction du voltage.

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A PELVIMETRIC METHOD FOR THE ASSESSMENT OF PELVIC 'MOULDABILITY'

by

Ulf Borell and Ingmar Fernström

To the best of the authors' knowledge, the 'mouldability' of the pelvis has hitherto not been taken into account in roentgenographic pelvimetry, probably because it has generally been believed that the pelvic dimensions undergo insignificant changes during labour, if at all. However, this does not seem to be true. In an investigation of 40 normal deliveries, the writers found that in the majority of cases the pelvic dimensions altered considerably during labour. These changes were disclosed by mensuration of the sagittal and transverse diameters of the pelvis from roentgenograms taken during labour (BORELL and FERNSTRÖM 1957).

Changes in the pelvic dimensions during labour

Changes resulting from rotary movement round a transverse axis at the sacro-iliac joints. It was found that movement round a transverse axis occurred at the sacro-iliac joints at the time of the passage of the foetal head through the inlet. This movement resulted in downward rotation of the innominate bone and in a slight increase of the true conjugate diameter, amounting in no case to more than 10 mm (Fig. 1).

At the time of the passage of the foetal head through the outlet the innominate bone was displaced upwards by a rotary movement, which resulted in a considerable increase in the sagittal diameter of the outlet. As a rule, this diameter increased by more than 10 mm and in a few cases by as much as 20 mm (Fig. 1).

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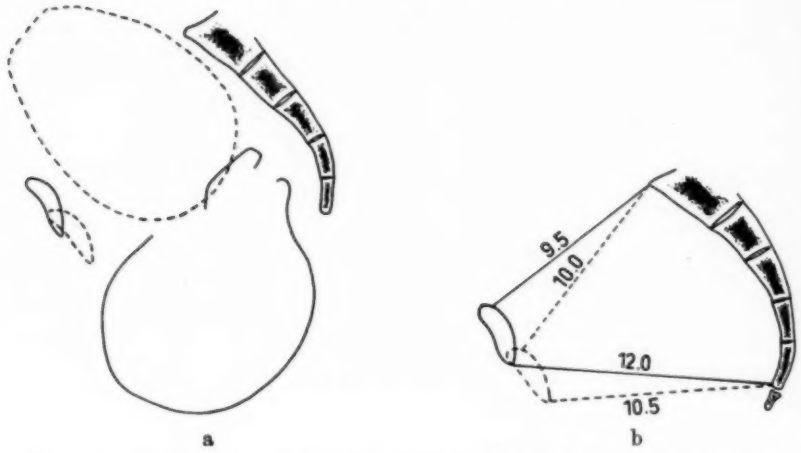

Fig. 1. a) Changes in the pelvic dimensions during labour. Broken line: Position of symphysis pubis and foetal head at time of passage of latter through pelvic inlet. Continuous line: Position of the symphysis pubis and the foetal head at time of passage of latter through pelvic outlet. b) Changes in sagittal diameters due to mouldability of pelvis. Broken lines represent true conjugate and sagittal diameter of pelvic outlet at time of passage of foetal head through pelvic inlet. Continuous lines represent true conjugate and sagittal diameter of pelvic outlet at time of passage of foetal head through pelvic outlet.

Changes due to widening of symphysis pubis and sacro-iliac joints. It was found that the transverse pelvic diameters did not increase in the majority of cases examined. In a few cases widening of the symphysis pubis and sacro-iliac joints was noted whilst the foetal head passed through the bony pelvis which resulted in an insignificant increase of these diameters, amounting in no case to more than a few millimetres.

The changes in the pelvic dimensions due to rotary movement round a transverse axis at the sacro-iliac joints appear to play a more important part in the mouldability of the pelvis than widening of the symphysis pubis and the sacro-iliac joints. It should be mentioned, however, that the present series included a few cases in which the pelvis dimensions did not undergo any changes during labour and pelvimetry carried out a few days after delivery by the technique to be described did not disclose any changes either. This observation suggests that there are cases in which the pelvis is 'non-mouldable'.

In a few cases the mobility of the sacro-iliac joints was found to be greater a few days after delivery than during labour. This suggests that movement at these joints is made full use of only in cases of contracted pelvis.

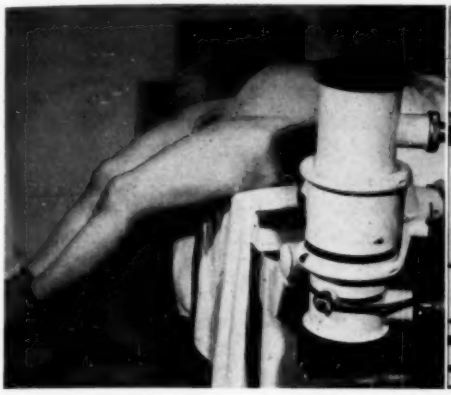

Fig. 2. Patient in Walcher's position.

Fig. 3. Patient in dorsal recumbent position with knees supported. Fluorescent screen of couch is used as support under the knees and raised to such a level that the buttocks are slightly raised.

Assessment of mouldability of pelvis prior to labour

During labour changes in the pelvic dimensions occur irrespective of the position of the patient. On the other hand, prior to labour alteration of the pelvic dimensions depends on the position of the patient. The present investigation was carried out to determine two positions resulting in the greatest degree of downward and upward rotation of the innominate bone respectively.

1. It was found that the greatest degree of downward rotation of the innominate bone occurred in Walcher's position, *i. e.* dorsal recumbent position, with the hips at the edge of the couch and the legs hanging down (Fig. 2).

2. A marked upward rotation of the innominate bone was observed in different positions. Three of these were compared with respect to the degree of the associated upward rotation of this bone, *i. e.* the patient was examined (1) in the erect position, (2) in the lithotomy position — supine, with the hips flexed and abducted, and the knees flexed — and, (3) in the dorsal recumbent position with the hips flexed about 90° and the knees supported. The support under the knees is elevated to such a level that the buttocks are slightly raised from the couch (Fig. 3). It was found that this latter position was generally associated with the greatest degree of upward rotation of the innominate bone.

Method of examination

Two lateral films of the pelvis are taken, one in Walcher's position (Fig. 2) and the other in the dorsal recumbent position with the knees supported (Fig. 3). Assumption of the latter position presents no difficulty if the fluorescent screen of the couch is used to support the knees in such a way that the buttocks are slightly raised off the couch. The films are taken in the horizontal projection with the overcouch tube. The cassette, which is fitted with a grid, is placed vertically on the couch and the central ray directed towards the acetabulum. In order to ensure comparability of films care should be taken that the pelvis has the same projection in the two exposures. A metal bar, graduated in centimeters and placed between the labia majora, enables the sagittal diameters to be measured directly from the film.

The true conjugate and the sagittal outlet diameter (distance between the sacro-coccygeal joint and the lower border of the symphysis) are measured from the films taken (1) in Walcher's and (2) in the dorsal recumbent position with the knees supported. The figures obtained are compared and the difference between each diameter in these two positions gives an idea of the mouldability of the pelvis. The greater the difference the greater the mouldability. Where these diameters are not altered it may reasonably be assumed that the pelvis is 'non-mouldable'.

The clinical value of the method

Where routine roentgenographic pelvimetry discloses normal pelvic dimensions and the possibility of cephalo-pelvic disproportion can be excluded, investigation of pelvic mouldability is naturally not required. However, where contracted pelvis or cephalo-pelvic disproportion is suspected and the sagittal diameters are small it is expedient to assess the mouldability of the pelvis by the technique described.

Since pelvic mouldability has been assessed in conjunction with routine pelvimetry in this clinic, cases have been encountered in which films taken in the lateral decubitus position with a vertical beam showed the sagittal diameter of the outlet to be 9 cm, and assessment of the mouldability of the pelvis (by the technique used in this investigation) disclosed that movement at the sacro-iliac joints resulted in an increase, varying between 1.5 and 2 cm, in this diameter. The resulting uncomplicated course of labour proved that there had not been outlet contraction. On the other hand, cases were observed where routine pelvimetry showed the sagittal diameter of the outlet to be 9 cm and the special technique revealed that no movement occurred at the sacro-iliac joints. The diagnosis of a narrow outlet was made from those findings and the

course of labour proved that the dimensions of the outlet had been correctly assessed.

It is interesting to note that in two cases in which a previous pregnancy had been terminated by Caesarean section because the sagittal diameter of the outlet had been judged by routine pelvimetry as being reduced, investigation of the mouldability of the pelvis at the end of a new pregnancy showed the sagittal diameter of the outlet to be adequate for delivery. Both patients had an uncomplicated delivery per vias naturales.

As already mentioned, assumption of the erect position is associated with upward rotation of the innominate bone, resulting in an increase of the sagittal diameter of the outlet and in a decrease of the true conjugate. As a rule, the figure for the sagittal diameter of the outlet obtained from films taken in the lateral erect position is slightly higher than that obtained from films taken in the lateral decubitus position. The risk of an erroneous diagnosis of outlet contraction is therefore greater where lateral films are taken in the latter position. A disadvantage of lateral films erect is that the figure obtained for the true conjugate is somewhat lower than that obtained from corresponding films taken in the lateral decubitus position. Moreover, it has been shown in this investigation that the maximum figure for the sagittal diameter of the outlet is obtained in the dorsal recumbent position with the knees supported and not in the erect position.

SUMMARY

The pelvis dimensions, particularly the sagittal diameters, and of these above all the sagittal diameter of the outlet, undergo marked changes during labour. A roentgenographic technique is described which permits investigation of the 'mouldability' of the pelvis prior to labour and enables a more reliable prognosis to be given as to its course.

ZUSAMMENFASSUNG

Die Bäckendimensionen, besonders die sagittalen Durchmesser und von diesen vor allem der sagittale Durchmesser des Beckenausganges, unterliegen während einer Belastung bedeutenden Schwankungen. Eine röntgenologische Technik wird beschrieben, die eine Untersuchung der Formbarkeit des Beckens vor der Belastung gestattet und eine zuverlässigere Prognose ihres Verlaufes ermöglicht.

RÉSUMÉ

Les dimensions du bassin, en particulier les diamètres sagittaux, et parmi ceux-ci surtout le diamètre sagittal du détroit inférieur, subissent au cours du travail d'importantes modifications. Les auteurs décrivent une technique radiographique qui permet d'étudier la 'plasticité' du bassin avant le travail et permet de porter un pronostic plus exact sur son évolution.

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ENLARGEMENT OF SPLEEN IMMEDIATELY AFTER WATER LOAD

Preliminary communication

by

Lars Andrén

In a roentgenologic investigation of the kidneys for any change in size following the intake of a large amount of fluid it was incidentally observed that immediately after the ingestion of 1 litre of water the spleen increased considerably in size, sometimes to more than twice its original volume, and then gradually returned to normal. This enlargement was seen in all projections.

Figs. 1 and 2 show roentgenograms of a spleen before and immediately after the subject had drunk 1 litre of water.

This observation prompted further investigation in which it was observed that this transient enlargement occurred regularly in normal subjects; that the increase was as a rule larger in young than in elderly individuals; that the enlargement was sometimes seen after the intake of as small a quantity of water as 300 ml; that the enlargement diminished or disappeared as soon as the subject got up, but reappeared as soon as he lay down again; that in certain diseases such as liver cirrhosis, leukemia, and mononucleosis with splenomegaly as well as in 3 cases of hepatitis studied, the phenomenon did not appear, but it did occur in Felty's syndrome and in hemolytic anemia with splenomegaly.

Comments

Although it is not yet possible to offer any definite explanation for the underlying mechanism of this phenomenon, the ingestion of such a

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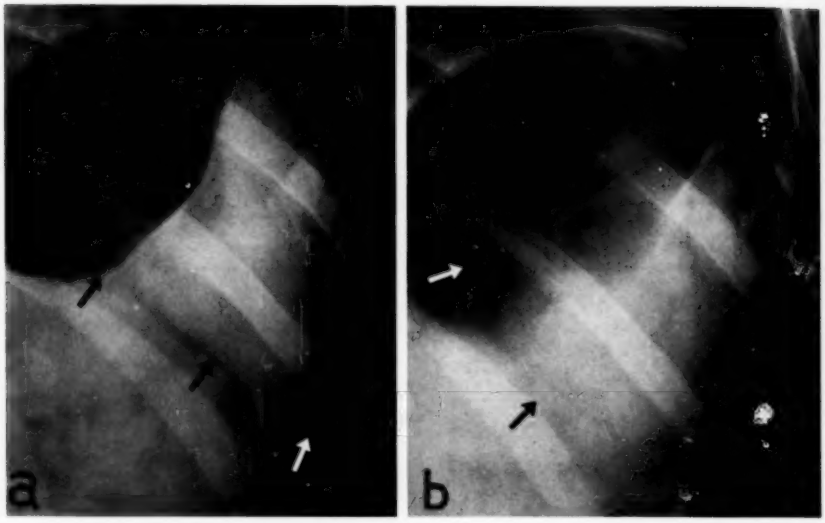

Fig. 1. Roentgenograms of male, aged 24, taken (a) before and (b) immediately after water load. Prone.

relatively large amount of water may increase the flow of blood through the portal system and thereby the portal pressure. This possibility is supported by the finding that the enlargement diminished considerably or disappeared as soon as the subject assumed the erect posture. The decrease in size on change of posture is probably due to the decrease in hydrostatic pressure in the splenic vein.

The possible differential diagnostic value of the phenomenon, particularly in the investigation of diseases with associated splenomegaly, and of portal hypertension, is receiving attention and the results obtained will be the subject of a future paper.

SUMMARY

The normal spleen apparently increases considerably in size immediately after the ingestion of a relatively large amount of fluid. The possible utilisation of this phenomenon as a differential roentgen-diagnostic tool is discussed.

ZUSAMMENFASSUNG

Die normale Milz nimmt unmittelbar nach der Verzehrung ziemlich grosser Flüssigkeitsmengen beträchlich an Grösse zu. Die Möglichkeit dieses Phänomen als ein röntgendiagnostisches Differentialdiagnostikum zu benutzen, wird diskutiert.

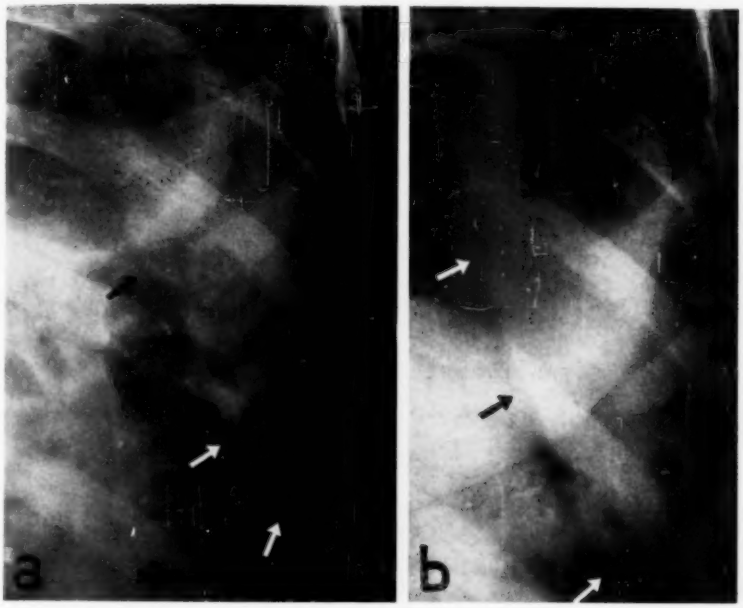

Fig. 2. Roentgenograms of male, aged 38, taken (a) before and (b) immediately after water load. Prone.

RÉSUMÉ

La rate normale augmente manifestement de volume d'une façon considérable aussitôt après l'ingestion d'une quantité relativement importante de liquide. L'auteur examine la possibilité d'utiliser ce phénomène comme moyen de diagnostic différentiel radiologique.

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DISCREPANCIES BETWEEN DEPTH DOSE DATA

A comparison between Grebe-Wiebe's and Johns' tables

by

Martin Lindgren

For many years extensive investigations have been performed to assess optimal doses in the radiologic treatment of different types of tumours. In these investigations the tumour dose has been calculated with the help of depth dose tables or determined by measurement in the irradiated region. Apart from tumours of the skin the latter method is possible only for a few deep tumours such as those situated in the esophagus (LIDÉN 1948). Depth dose tables have therefore found wide use.

In the calculation of the tumour doses in a brain tumour series from our department, use was made of Grebe-Nitzge's tables (1930) and later of Grebe-Wiebe's tables (1950). Using a skull phantom with the soft parts substituted by tissue equivalent material 'Mix D' (JONES and RAINE 1949), the intracranial distribution of the dose measured was found to differ appreciably from that calculated with the use of these depth dose tables.

This observation prompted a closer analysis of the reliability of our clinical methods for calculation of the dose and a comparison of our tables with others of recent data. The investigation was limited to the data employed for our therapeutic technique (FSD 50 and 60 cm, HVL 1.0 or 1.5 mm Cu, 170 kV).

Technique. The field to be treated was limited directly on the skin by lead rubber plates with 2 mm lead equivalence which protected the rest of the skull as well as the upper portion of the trunk. Irradiation was

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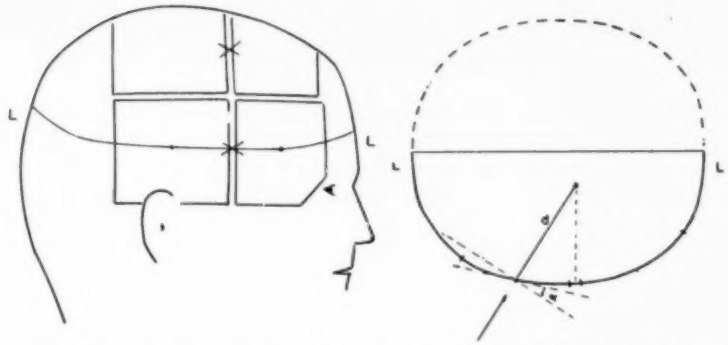

Fig. 1. Technique usually employed in the treatment of hemisphere tumours and in the calculation of tumour doses. Crosses (×) indicate two perpendicular projections of the tumour centre on the skin. d = distance between middle of field and centre of tumour. α = angle between field plane and a plane perpendicular to central beam.

adjusted with the help of indicator points obtained by projecting the centre of the tumour onto the skin in the horizontal and sagittal planes (Fig. 1). Tubes were used only exceptionally. With this technique treatment can be repeated with the same radiation direction on all occasions.

Calculation of tumour doses. Hemisphere tumours were treated via 4 fields distributed in such a way that the border between the anterior and posterior pair was located in an approximately frontal plane passing through the centre of the tumour. The outline of the skull in a plane through one of the above mentioned projections of the centre of the tumour onto the skin and the middle of each field is determined by means of a suitable contour follower. Then the distance between the middle of the field and the centre of the tumour is determined graphically (Fig. 1). The diagram also gives the angle of projection α, necessary for estimation of the projection of the field onto a plane perpendicular to the central beam. The relative depth dose for each field was determined with the help of depth dose tables, allowance being made for the effective size of the irradiated skin surface; only the doses at the point of intersection of the central rays of the four fields were calculated, the percentages given in the depth dose tables referring to these. The accuracy of calculations is impaired by approximation. Owing to the curvature and small volume of the skull as well as to the obliquity of the beam, the contribution to the dose from the scatter is smaller and at the same time asymmetric. Varying thickness of the bone of the skull also contributes to errors in the calculation of the depth dose.

Despite these obvious but fairly small sources of error, this simple method of calculation of the dose has been considered accurate enough for clinical use.

Comparison between measured and calculated dose. In this comparison the depth doses were calculated with the help of GREBE-WIEBE's tables and JOHNS' tables (1953) in the Central Axis Depth Dose Data, Section 3.

Grebe-Wiebe's tables (1950), which represent a revised edition of Grebe-Nitzge's tables (1930), contain a critical review of depth dose measurements available. It is pointed out that relatively few measuring results have been published during the years 1930—1949 and that the lack of agreement between the values obtained by different authors makes further investigation with modern methods desirable. All depth doses in these tables are based on measurements made in water phantoms. No data are given of the size of the phantom, the measuring chambers used, or the manner of shielding.

Johns' tables are based on measurements in an iron tank filled with water and measuring 60 × 40 cm with a depth of 30 cm. A specially constructed small wavelength independent measuring chamber and circular fields were used. The desired field size and focus—skin distance are obtained with the help of specially constructed open-ended galvanised iron applicators. The field is limited by means of a lead diaphragm 4 cm above the surface of the phantom and again above this two similar arrangements to eliminate undesired penumbra and scatter, are placed.

A comparison between these Canadian measuring values and the English values with closed-ended applicators was made at the initiative of the Hospital Physicists Association (H. P. A.) in England. After application of a correction method no systematic difference was found. It was therefore suggested that the values given by Johns should be taken as standard for open-ended applicators. The tables are given in Section 3 of the Central Axis Depth Dose Data (1953).

With our method of treatment, Johns' tables can be used for depth dose calculation. In an investigation of the effect of the diaphragmatic system on the relative depth dose COHEN (1955) showed that the walls of the applicator have but little influence on the relative depth dose. When using small fields the position of the diaphragm in relation to the focus is all the more important because of the effect of the penumbra. As mentioned, in our department we do not use applicators but limit the field on the skin; thus no penumbra effect occurs in the treatment fields. The penumbra is also limited in Johns' experimental arrangement, and because the influence of the wall of the applicator is negligible and the effect of the penumbra is eliminated in both cases, Johns' table should be suitable for our therapeutic technique.

For comparison between the measured and the calculated relative

depth dose an intracranial point in the above-mentioned skull phantom was selected, from which the distance to the middle of all four fields was 6 cm. It was assumed that every field was irradiated with the same surface dose. The field size was 35 to 65 cm². The calculated depth doses were reduced by the factor 0.94 to allow for bone absorption. The measured doses were 198 % of the surface dose, and the calculated doses according to Grebe-Wiebe 160 % and to Johns 183 %.

It is apparent that obvious differences can be demonstrated between the measured and the calculated total depth dose percentages as well as between the values calculated from the two different tables. In the selected point the calculated doses differed by 19.2 per cent and 7.6 per cent from that measured. These deviations are due to the above-mentioned sources of error in the clinical assessment of the dose, which are equal for both tables and secondly, to differences in the sizes of the doses given in the two tables. The difference 7.6 per cent between our measured doses and those calculated from Johns' tables can probably be ascribed entirely to the difficulties in clinical estimation of the doses.

Comparison between depth dose data tables. For this comparison the half-value layer 1.0 mm Cu or 1.5 mm Cu was used, which corresponds to our filtration with 0.5 mm Cu + 1 mm Al (or tin filter according to Thoraeus = 0.4 mm Sn + 0.25 mm Cu + 1 mm Al) at 170 kV. A field size of 50 cm² was selected, this corresponding to the average size we use in the department (Table 1).

Table 1

Comparison between Grebe-Wiebe's and Johns' percentage depth doses. FSD 50 cm. Field size 50 cm²

Depth cm	1.0 mm Cu HVL			1.5 mm Cu HVL		
	Grebe-Wiebe	Johns et coll.	Diff. %	Grebe-Wiebe	Johns et coll.	Diff. %
1	100	98.2	— 2	101	98.0	— 2
2	84	90.2	7	85	90.5	6
3	72	80.5	12	74	81.4	10
4	62	70.6	14	63	71.5	13
5	54	61.1	13	55	62.3	13
6	47	52.5	12	48	53.8	12
7	41	45.0	10	41	46.4	13
8	34	38.2	12	36	39.8	11
9	30	32.5	8	31	34.1	10
10	26	27.8	7	27	29.3	9
11	22	23.7	8	23	25.0	9
12	19	20.1	6	20	21.4	7
13	17	17.0	0	18	18.3	2
14	15	14.4	— 4	16	15.7	— 2

Grebe-Wiebe's tables give a much lower percentage of depth dose than Johns' tables for depths of 2 to 12 cm. The largest difference observed

between these was 14 per cent. For depths of less than 2 cm and more than 13 cm (Diagram 1), *i. e.* within a region of less clinical importance in the treatment of brain tumours, Grebbe-Wiebe's tables give higher percentages than Johns' tables.

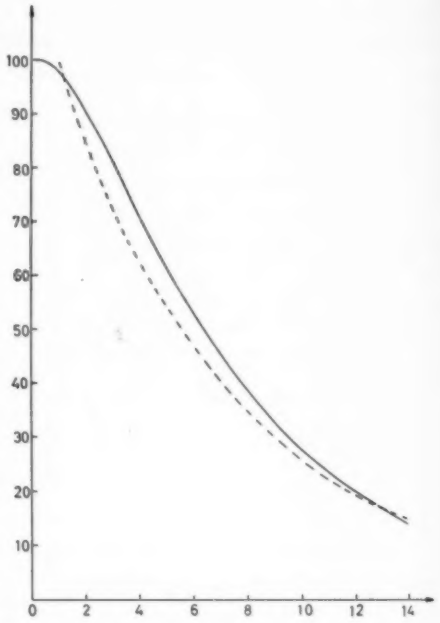

Diagram 1. Graphical comparison between percentage depth doses in Grebe-Wiebe's (— — —) and Johns' tables (———). HVL 1.0 mm Cu. FSD 50 cm. Field size 50 cm².

Discussion

The experimental values found for the relative depth dose agree well with the corresponding values given in Johns' tables. The difference demonstrated can be ascribed essentially to the above-mentioned sources of error in the clinical method of assessing the doses.

Our measurements were made in the solid phantom material Mix D and not, as in the both tables under discussion, in water. Extensive comparisons have been made by JONES and RAINE (1949) between water and Mix D phantoms. The investigation included four half-value layer regions (HVL) between 0.6 mm Al and 1.05 mm Cu. The scattered radiation partly on the surface and partly deeper in a region with only scattered radiation, as well as the axis dose at a depth of 5 cm, were measured. The results were that the maximum variation between Mix D and water lay within the limits of the error of the method and was therefore negligible. The same observations were made by JENNINGS (1952) for the HVL region 1.93 to 0.042 mm Al. He found, however, that with an HVL lower than 0.145 mm Al a small difference began to appear.

The results of personal measurements and those given in Johns' tables refer to comparable techniques. Both these investigations were carried out by refined modern measuring methods. It is thus apparent that the Grebe-Wiebe's tables cannot be used for calculation of the depth dose with the qualities of rays and treatment technique employed by us.

It should be observed that on comparison between Grebe-Wiebe's tables and H. P. A. tables, COHEN (1956) found distinct differencies also for closed-ended applicators (Central Axis Depth Dose Data, Section 2).

In an investigation of depth doses in the treatment of gynecologic diseases RIESSBECK (1955) found the doses measured to vary widely in both directions from those calculated by Grebe-Wiebe's tables. No regular tendency was noted and therefore no correction factor could be applied. He assumes throughout that the doses measured are the correct ones and concludes that the deviations are due to a number of factors preventing satisfactory clinical calculation of the dose. He does not question the correctness of Grebe-Wiebe's tables although the difficulties in interpretation might possibly be due to the use of these tables.

Grebe-Wiebe's tables have, however, been used for several years for the calculation of tumour doses. As shown before it is apparent that the calculated dose in the centre of the tumour located at a depth of 6 cm from all four fields of treatment is 19.2 per cent lower than the dose measured. Determination of a desired tumour dose of 6,000 r according to GREBE-WIEBE would in this case in reality give a dose 24 per cent higher, *i. e.* about 7,400 r. Our clinical material contains examples of such overdosage found on reexamination, which may help to explain certain complications. In the comparison of various radiotherapeutic methods and the results obtained in different hospitals in the management of tumour diseases, much importance is attached to the size of the tumour dose. As is apparent from the observation above, any discussion of the depth doses is of less importance as long as tables are used which give relatively different values.

The clinical importance of reliable depth dose data has been stressed by BODEN (1952) and COHEN (1955). The use of uniform tables made with extreme precision and based on modern accurate measuring methods is a necessary requirement. Until this want is fulfilled, authors should always indicate the tables they have used.

SUMMARY

In an investigation of the intracranial distribution of the dose differences were found between the experimental data and those obtained from depth dose tables. The difference in the relative depth dose between that measured and that calculated from Grebe-Wiebe's tables was remarkably large, while the doses calculated with Johns' tables showed good agreement. The clinical importance of reliable depth dose tables is stressed.

ZUSAMMENFASSUNG

Bei einer experimentellen Untersuchung der intrakraniellen Dosisverteilung wurden Differenzen zwischen den Messwerten und den aus Tabellwerken ermittelten Tiefendosen beobachtet. Der Unterschied zwischen den relativen Tiefendosen der gemessenen und der mit Hilfe von Grebe-Wiebe's Tabellen berechneten Werte war ziemlich gross, während die aus Johns' Tabellen erhaltenen Dosen gut mit den Messwerten übereinstimmten. Die klinische Bedeutung zuverlässiger Tabellen zur Dosierung der Röntgenstrahlen wird hervorgehoben.

RÉSUMÉ

Un travail de recherche sur la répartition des doses de rayons roentgen dans le crâne a montré des différences entre les données expérimentales et celles que fournissent des tables de dose en profondeur. La différence entre la dose relative en profondeur mesurée et celle calculée à partir des tables de Grebe-Wiebe était considérable, alors que les doses calculées au moyen des tables de Johns présentaient une bonne concordance. L'auteur insiste sur l'importance clinique de tables de dose en profondeur exactes.

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MALIGNANT TUMOURS AND SARCOID REACTIONS IN REGIONAL LYMPH NODES

by

Gunnar Gorton and *Folke Linell*

Tuberculoid granulomatosis of obscure origin is becoming an ever increasing problem. However, there appears to be general agreement that a distinction must be maintained between the generalised disease *sarcoidosis* (Morbus Besnier-Boeck-Schaumann or lymphogranuloma benignum) and localised changes of the same histologic type — *sarcoid reaction*. (The authors are fully conscious of the word 'sarcoidosis' being a bad one. Its use has, however, been so widespread that it would be impossible to eradicate it.) This was clearly pointed out by NADEL & ACKERMANN (1950). In some cases, however, it might be difficult to decide whether a change of sarcoid type should be regarded as a localised lesion or as a manifestation of a generalised disease. It has long been known that more or less widespread epithelioid granulomatosis may sometimes be seen in lymph nodes regional to malignant tumours (NADEL & ACKERMANN 1950, SYMMERS 1951, GORTON 1953). The present paper is concerned with an analysis of cases of this type observed by us during the last few years. Some of the cases were reported in brief elsewhere (GORTON 1953). Several authors have suggested that the sarcoid changes in the lymph nodes might be regarded as a reaction against metabolic or disintegration products from the tumour. This hypothesis might be supported by the fact that most of the cases observed by us were seen in patients who had received radiation treatment for squamous cell carcinoma of the uterine cervix. We tried to reproduce similar conditions experimentally by inducing tumours in rabbits by the administration of carcinogenic hydrocarbons and studying the regional lymph nodes.

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Clinical study

In the material received at the Department of Pathology, all those cases of malignant tumour were recorded in which sarcoid changes were observed simultaneously in the regional lymph nodes. Our material covers the years 1945—1954. The composition of the material is given in Table 1.

Table 1

Localisation	Number of cases	Number of cases irradiated
Carcinoma of uterine cervix	24	24
Carcinoma of mammary gland	7	3
Carcinoma of other localisations	7	4
Total	38	31

It is apparent from the table that the majority of cases consisted of cervical cancer. As to other localisations, mammary cancer dominated with its 7 cases. The other cases consisted of parotid carcinoma, bronchial carcinoma, squamous cell carcinoma of the skin and of the vulva, respectively, adenocarcinoma coli, uterine sarcoma and one case of malignant melanoma of the skin. It is clear from the table that all of the cases of uterine cervical carcinoma had been treated radiologically.

Radiotherapy consisted of a combination of intracavitary radium treatment and roentgen therapy given externally. Treatment was fractionated and protracted over a period of four weeks. The total radium dose was 7,200 mg/hr. Supplementary roentgen treatment, 3 × 500 skin r per field was given via 2 anterior fields and 2 posterior fields to the outer parts of the parametria and the lymph nodes along the pelvic walls.

When the local tumour has healed clinically, it has been the rule since 1948 to extirpate the pelvic lymph nodes. During the years 1948—1949 the operation was carried out 2 months and later 4 months or longer after conclusion of radiologic treatment. During the years 1948—1954 this supplementary operation was performed on a total of 305 cases. In 24 (7.9 per cent) of the cases the lymph nodes showed changes of a sarcoid type. In 40 (13.1 per cent) cases metastases were demonstrated in the lymph nodes. All 24 patients with lymph nodes of sarcoid type were examined for the possibility of generalised sarcoidosis. However, none showed skin changes or palpable lymph nodes in the groins, axillae, or supraclavicularly. Roentgenography of the chest and examination of the eyes revealed no abnormality; roentgenography disclosed no bone changes. All the patients were tuberculin positive (0.05 mg to 0.1 mg). Electrophoresis showed in the main normal serum protein fractions. The E. S. R. never exceeded 20 mm/1 hr. On the other hand, the cutaneous sarcoid tissue test (Kveim's reaction) was not carried out. The youngest of the

patients was 33 years old, the oldest 55 (mean 43.4 years). Table 2 gives the duration of follow up and the results achieved in this group of patients.

Table 2

	Number of cases	Deaths
1948	1	0
1949	1	0
1950	5	1
1951	2	1
1952	6	3
1953	6	0
1954	3	0
	24	5

Of these 24 patients, then, 5 died (2 from local recurrences and 3 from remote metastases with locally healed tumour). The remainder are still alive (1956); they feel well, carry on with their work, and have no symptoms. None of the survivals received irradiation therapy after extirpation of the regional lymph nodes.

The number is too small to permit any valid conclusions about the results compared with cases without sarcoid changes. The results are, however, at any rate not poorer than those achieved by others in the treatment of uterine cervical carcinoma.

Histologic data

Since the bulk of the material consisted of specimens from lymphonodectomy of irradiated patients with uterine cervical carcinoma, this group will be dealt with first. Of these 24 patients, only 2 showed metastatic growths. Macroscopically the lymph nodes were as a rule only slightly enlarged and seldom exceeded the size of an almond. They were fairly firm in consistence and in most cases showed no appreciable macroscopic changes. Histologically, all of them presented a more or less pronounced picture of sinus catarrh, the sinuses being widened and filled with pale-staining endothelial cells. The lymph nodes were on the whole poor in lymphocytes and often showed pronounced connective tissue sclerosis. The latter changes were, however, seen in all lymph nodes from this surgical material. A characteristic change was the occurrence of circumscribed epithelioid cell granulomas. They were built up of large pale-staining cells with foamy cytoplasm and vesicular nuclei with distinct nucleoli. These epithelioid cell foci were sometimes sparse, only one or two small foci being seen when examining a large number of lymph nodes

Fig. 1. Pelvic lymph node from case of uterine cervical cancer. Marked sinus catarrh with network of pale broadened sinuses. Epithelioid cell granuloma indicated by arrows.

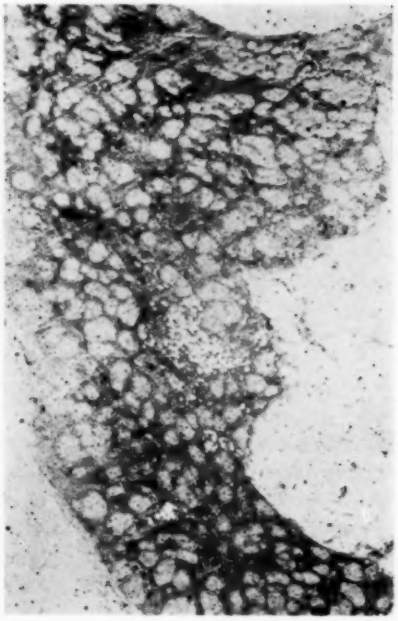

Fig. 2. Pelvic lymph node from case of uterine cervical cancer. The lymph node is studded with small epithelioid cell granulomas.

(Fig. 1). In other cases all lymph nodes contained epithelioid cell foci and in extreme cases all of the lymph nodes contained numerous epithelioid cell foci (Figs. 2 and 3). Confluent tubercles forming conglomerates were not uncommon, but as a rule the epithelioid cell foci were discrete and, broadly speeking, the lymph nodes hardly ever contained closely packed tuberculoid foci. Sometimes lymph nodes in one localisation contained abundant foci, while other nodes from the same patient were free from such changes.

In many cases gradual transitions were discernible between the sinus catarrh mentioned and the occurrence of epithelioid cell foci (Fig. 4). The cells in the sinus often closely resembled epithelioid cells, and sometimes it was seen how the sinus became wider and its content of cells merged in a round tubercle-like epithelioid cell focus. Epithelioid cell foci were, however, often seen centrally in lymph follicles.

In addition to tubercle-like epithelioid cell foci so-called patchy re-

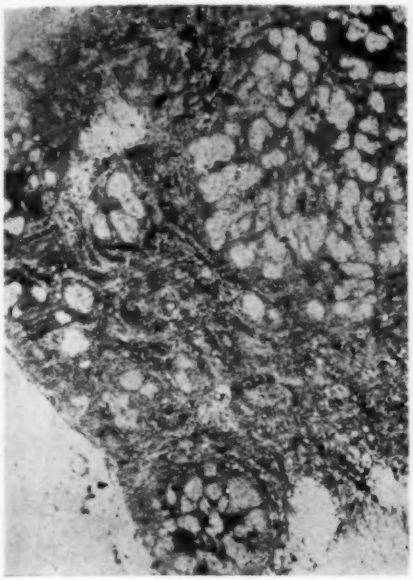

Fig. 3. Pelvic lymph node from case of uterine cervical cancer. Some parts show groups of epithelioid tubercles; others, only sinus catarrh.

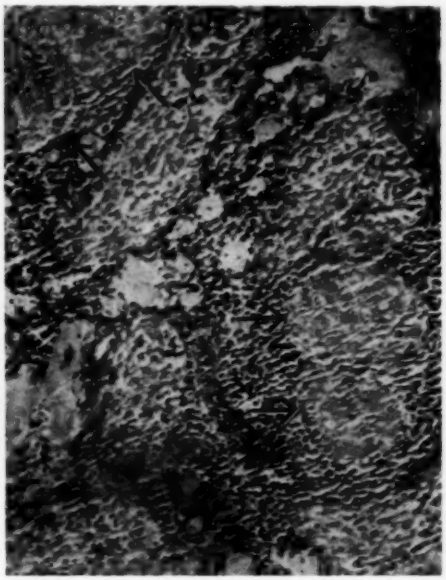

Fig. 4. Pelvic lymph node from case of uterine cervical cancer. Note gradual transition from sinus catarrh and epithelioid granulomas (arrows).

ticulosis was sometimes seen (Fig. 5) this being associated with large pale-staining epithelioid cell-like elements in the shape of ill-defined groups of a few cells. All degrees of transition were seen between such groups of cells and typical tubercular structures.

The foci often contained a varying number of giant cells (Fig. 6). Giant cells of Langhan's type as well as of a foreign body type were noted. In 5 of the 24 cases inclusion bodies were observed inside the giant cells in the form of dark concentrically layered masses which in appearance agreed with so-called Schaumann-bodies (Fig. 7). These often showed marked pyroninophilia. In one case a typical asteroid body and in others, spiral thready structures were noted. In the vicinity of the latter were spaces of the type seen after the dissolution of fatty substance. In most cases the epithelioid cell foci were completely free from necroses and only in 2 of the cases were single small necrotic foci of fibrillar type observed. In 2 of them lymphonodectomy had been performed 4 and 5 months, respectively, after the conclusion of radiologic treatment. In none of the cases were acid-fast bacilli seen in Ziehl-Neelsen stained sections.

In other cases in which a cancer was extra-uterine the histologic

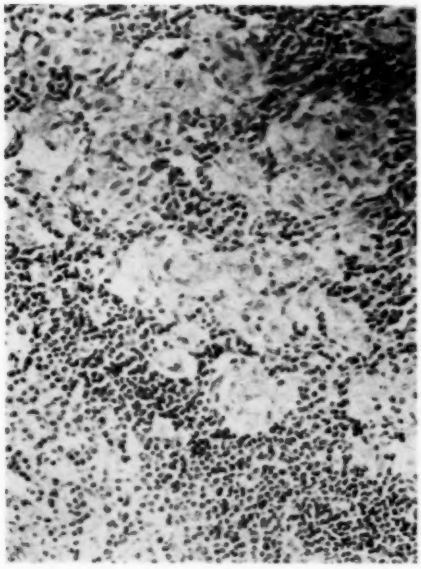

Fig. 5. Patchy reticuloses with gradual transition to epithelioid tubercles.

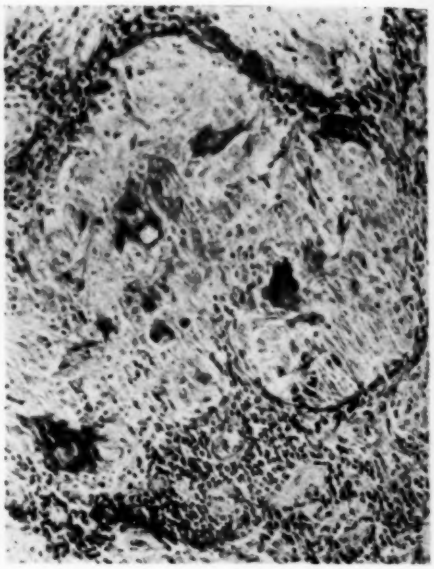

Fig. 6. Epithelioid granulomas with numerous giant cells.

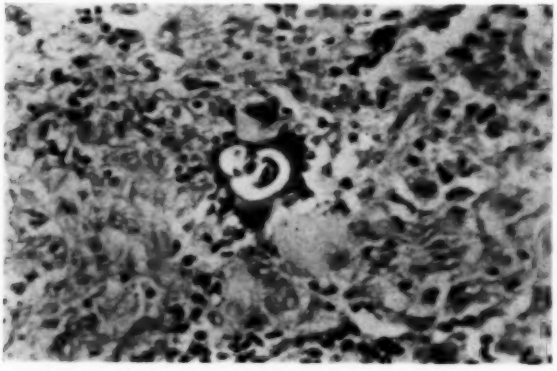

Fig. 7. Giant cell with laminated inclusion (Schaumann body).

preparations in the main revealed the same changes. It should, however, be pointed out that in as many as 8 of these 14 cases the epithelioid cell foci showed necroses. In 7 of the cases the necroses were fibrillar and in a few of the caseous type. Acid-fast bacilli were not demonstrable in the sections. Five (5) of the cases showed more or less marked hyaline bands in or round the foci. In 4 of the cases Schaumann bodies were seen.

Experimental study

Methods and material. The material consisted of 20 market rabbits, which weighed 2,000 to 3,000 g at the beginning of the experimental period. Two of the animals died relatively soon from intercurrent diseases. The series thus consisted of 18 rabbits.

The inside of both ears of each rabbit was painted twice a week with 0.5 % 9,10-dimethyl-1,2-benzanthracene in acetone. The rabbits reacted to the carcinogenic agent in the way described earlier (LINELL & NORDÉN 1950). During the third week small tumours began to appear, and after 5 weeks all the animals had tumours, although in widely varying number. During 12 weeks the ears were painted altogether 24 times. By the end of the painting period nearly all the animals had several tumours in both ears (only 2 of the animals had only a few small tumours). Most of the animals had up to walnut-sized fleshy tumours. The surface of the tumours was often macerated and smeary, and foul-smelling masses of detritus often occurred between the larger tumours.

After the painting period the inside of the right ear was irradiated. Radiation was delivered to a 10 × 5 cm field, which about covered the tumourous part of the ear. The other ear and the rest of the head were protected with a 3 mm lead mask. The irradiated field received a skin dose of 2,250 r in a single dose. In connection with irradiation 3 animals were lost because of spinal fracture. Five (5) animals were killed 3 weeks after irradiation. Eight weeks after the first dose the remaining animals received a further dose of 1,300 r to the inside of the right ear. They were then killed after a varying interval. The last 3 were killed 11 weeks after the final dose.

The animals were examined post mortem, histologic examination of the ears and ear lymph nodes being included. The auricular lymph nodes were cut into slices 2 mm thick which were embedded in paraffin and sectioned. Specimens from 2 to 5 different regions of every ear were examined.

Results

As mentioned, all the rabbits except 2 had several and large tumours. They were of the earlier known type, *i. e.*, large villous papilloma with intermingled ulcerating carcinomatoids. Combinations of these types were common. True carcinomas in the biologic sense of the term also occurred, since many of the animals developed metastases in regional lymph nodes.

The effect of the irradiation was difficult to evaluate. In 7 of the animals, however, the tumours on the right ear showed distinct regression in size and number after radiation. In a further 4 cases regression was less certain. In 3 of the rabbits large necroses of the ear cartilage occurred with consequent shedding of large parts of the ear. On those ears not irradiated the tumour grew vigorously in all the animals except one, this also applying to the irradiated ear of 4 of the animals; 3 of these animals belonged to those that received roentgen irradiation on two occasions. As a rule, the regional lymph nodes were markedly enlarged and could often be palpated *in vivo*; at post mortem examination they were sometimes anything up to the size of a cherry and sometimes contained gross abscesses. The histologic examination revealed that the enlargement was usually due to inflammatory changes. The lymph nodes

showed general swelling of the reticular cells with sinus catarrh and massive plasma cell infiltrations were often seen. Especially when the tumours on the corresponding ear exhibited purulent inflammation, there were often abundant deposits of leucocytes in the lymph nodes and sometimes purulent liquefaction. Metastases were seen in the lymph nodes of 10 animals, in 2 of them on both sides, in 2 only on the right side, and in 5 only on the left side. Sometimes only a few scattered small marginal metastases were observed, but occasionally the lymph nodes were completely replaced by metastases in which pronounced keratinisation was frequently noted and widespread necroses often occurred. Adjacent necroses and horny masses inflammatory changes with granulomas containing foreign body giant cells were common. Nowhere, however, were tuberculoid granulomas seen of the type found in the human material.

Discussion

The simultaneous occurrence of cancer and tuberculoid structures has long been the subject of much interest. ROKITANSKY expressed the view that it occurred so seldom that it provided a basis for his theory that cancer and tuberculosis counteract one another in a dyscrasic way. This assumption was, however, later abandoned after the publication of numerous cases of cancer and tuberculosis in combination (for literature see KRISCHE 1913). In these published cases the patients often had cancer in combination with tuberculosis that was definitely genuine since widespread caseous necrosis and/or positive findings of acid-fast bacilli were common. However, the possibility cannot be excluded that in some cases the patients had cancer combined with tuberculoid reactions of other origin. This brings us to the problem of to-day, *i. e.*, cancer together with sarcoid reaction in the lymph nodes. Judging by recent papers (NADEL & ACKERMANN 1950, SYMMERS 1951), there appears to be fairly general agreement that the lesions in the lymph nodes are not truly tuberculous. The present material consisting of 38 cases provides further support for this opinion. It is true that culture and guinea-pig inoculation were not done, but in no case were any acid-fast rods found. Neither did clinical investigation reveal any tuberculous manifestations. It is, of course, not possible histologically to exclude tuberculosis in a given case, and the present material might also contain a few cases of tuberculosis. As to the vast majority of cases, however, lesions were probably tuberculoid granulations of non-tuberculous origin.

As mentioned in the introduction, the question under discussion is whether regional lymph nodes with tuberculoid granulations are manifestations of generalised sarcoïdosis (morbus Besnier-Boeck-Schaumann

or lymphogranuloma benignum) or whether they should be regarded as a strictly localised condition. The diagnosis of sarcoidosis is difficult to establish and the exclusion of all sorts of local sarcoid reactions requires a combination of several signs. In addition to the histologic picture it demands the demonstration of multiple lesions and of a chronic course. Furthermore, the tuberculin reaction is often weak or negative. Hyperglobulinemia is also common. Of our cases, only those with carcinoma of the uterine cervix were examined in these respects. As mentioned, in none of these cases did we find evidence suggesting that the tuberculoid changes in the pelvic lymph nodes were manifestations of generalised sarcoidosis. It would, of course, have been useful if lymph nodes from other parts of the body had also been examined histologically. This was possible in 1 case in which the patient died.

Postmortem No. 201/55. The patient was a woman aged 47 who had received radium treatment at the Department of Radiotherapy, for carcinoma of the uterine cervix, Stage II. In October 1952 the pelvic lymph nodes were removed. The lymph nodes contained wide-spread tuberculoid changes as in sarcoidosis. In 1954 roentgen examination revealed signs of lung metastases. The patient died in May 1955. Autopsy revealed cancer metastases in the para-aortal lymph nodes, lungs, liver, kidneys, and suprarenals. No tuberculoid changes were found in the lymph nodes from the groins, axillae, and peritoneal cavity. Neither was any scar formation observed that might be referable to earlier sarcoid changes.

There thus appears to be good reason to assume that the sarcoid reaction is a local manifestation and in some way or other dependent on the malignant tumour. A point of interest in this respect is whether the changes in these cases differ histologically from those seen in general sarcoidosis. Here, however, it must be concluded that they do not show any such pronounced features permitting their distinction from ordinary sarcoidosis lesions. In the large material of lymph node changes in carcinoma of the uterine cervix fibrillar necroses were strikingly rare in the tuberculoid foci. It is possible that this might have something to do with the age of the granuloma. Despite investigations of the development of sarcoid granulomas, it appears that nothing is known with certainty about the time of appearance of the necroses (Barrie & Bogoch 1953). In the present material the giant cells contained inclusion bodies, which did not differ in appearance or occurrence from what is seen in sarcoidosis. Of the inclusion bodies, those of Schaumann type were the most common.

In the single case then there is, as a rule, no possibility of deciding from the histologic picture whether the extirpated lymph nodes are due to local sarcoid reaction or generalised sarcoidosis. Nevertheless, it must be stressed that in genuine sarcoidosis the lymph nodes are often markedly enlarged and packed with epithelioid cell granulomas (Zettergren 1954). In the present material the lymph nodes were as a rule only slightly enlarged, and although histologic examination revealed numerous

epithelioid cell foci, they were never packed so closely as in genuine sarcoidosis.

Thus, in the absence of evidence suggesting generalised disease, it is most probable that it is a question of local sarcoid reaction. It has long been assumed that the tuberculoid granuloma develops as a reaction against products from cancer (SYMMERS 1951, REFVEM 1954). This view is supported by the not uncommon occurrence of tuberculoid granuloma in the stroma of malignant tumours such as squamous epithelial carcinomata of the skin. Tuberculoid structures have often been described in ovarian dysgerminoma (HELLER 1943). The possibility has been suggested that the changes in the lymph nodes occur as a result of cancer cells or disintegration products of cancer being carried by the lymph stream to the regional lymph nodes. It is difficult to decide whether whole cancer cells or only disintegration products reach the lymph nodes and give rise to granuloma. If the granuloma were the result of a reaction against whole vital cancer cells the occurrence of cancer together with metastases and tuberculoid granuloma should be common (sarcoid reaction). It is true that this has been described (FISCHER 1947, KAUFFMANN-STAEMMLER 1955), but it appears to be rare. In our relatively large material of 38 cases it was thus observed in only 4 (1 case of carcinoma mammae, 1 of carcinoma bronchiale, and 2 of carcinoma of the uterine cervix). As to our cases of carcinoma of the uterine cervix, metastases were seen in sarcoid lymph nodes with the same frequency as metastases occurred in the entire lymph node material. This rare coincidence of metastases and sarcoid reaction in the lymph nodes appears to argue strongly for a sarcoid reaction occurring as a consequence of disintegration products from cancer foci without it being necessary for entire vital cancer cells to be carried to the lymph nodes. Another observation favouring this interpretation is that the sarcoid reaction is much more common in carcinoma treated with radiation. The majority of our cases had received radiotherapy for uterine cervical carcinoma. The next largest group was that of carcinoma mammae, a form of cancer that is often treated radiologically before operation. Radiologic treatment is, however, not an absolutely necessary condition for the development of a sarcoid reaction, because both in our material and in others this reaction was seen in patients who had not been treated radiologically. That disintegration products from irradiated carcinoma is of causal significance in sarcoid granuloma is strengthened further by the studies of LARSSON (1949). He described 26 cases of tubercle-like structures which occurred in scars after irradiated skin carcinoma without signs of recurrence of the tumour.

Our experiments with 9,10-dimethyl-1,2-benzanthracene induced tumours aimed at experimentally reproducing the above-mentioned mode

of development. But the results were negative. Interesting in this connection was, however, the observation that the large, induced tumours were affected but slightly by irradiation and in most cases apparently not at all, despite the use of such large doses as are curative for skin carcinoma in human beings. However, in rabbit tumours of this type the cells undergo considerable destruction independently of radiation treatment. The absence of a sarcoid reaction in this series may be due to differences in the mode of reaction in man and in rabbit or to the experimental material being too small. Striking in the animal experiments was the abundance of metastases in the lymph nodes; inside the latter foreign body granulomas with numerous giant cells were common. These changes resembled those described by McGregor (1934) in man following radiotherapy of lymph node metastases of squamous epithelial cancer. However, these lesions did not resemble sarcoid reactions. Our experimental findings thus provided no direct support for the assumption that radiation contributes to the development of sarcoid reactions but strong evidence in this respect was produced by the fairly frequent occurrence of these reactions in patients who had received radiotherapy.

As to whether any special type of cancer is particularly liable to give rise to sarcoid reaction, it might be mentioned that it has often been observed in squamous epithelial carcinoma. In our material all carcinomata of the uterine cervix were of the squamous epithelial type, but that sarcoid reactions can also occur in other types of cancer was shown by their occurrence, for example, in adenocarcinomata of the mammary glands.

SUMMARY

In 38 cases of malignant tumours tuberculoid epithelioid cell granulomas were observed in the regional lymph nodes. Twenty-four of the cases had irradiated squamous epithelial carcinoma of the uterine cervix and were the subject of detailed clinical examination without signs of generalised sarcoidosis being demonstrable. The histological picture is described and it is concluded that epithelioid granulomas in the lymph nodes regional to malignant tumours are a localised sarcoid reaction probably due to disintegration products from the tumours. Attempts to reproduce sarcoid reactions in ear lymph nodes of rabbits by irradiation of skin tumours of the ear induced by carcinogenic hydrocarbons failed.

ZUSAMMENFASSUNG

In 38 Fällen mit malignen Tumoren wurden tuberkuloide Epitheloidzellengranulome in den regionären Lymphknoten beobachtet. Vierundzwanzig Fälle hatten bestrahlte Scheibenepithelkarzinome des Gebärmutterhalses; sie wurden Gegenstand einer gründlichen klinischen Untersuchung, ohne dass Anzeichen einer generalisierten Sarkoidose nachgewiesen werden konnte. Das histologische Bild wird beschrieben und es wird konkludiert, dass Epitheloidzellengranulome in den regionären Lymphknoten maligner Tumoren eine lokale Sarkoidreaktion darstellen, welche wahrscheinlich auf Zerfallprodukte der Tumoren beruht. Versuche, die sarkoide Reaktion in Ohrenlymphknoten von Kaninchen durch Bestrahlung von Ohrenhauttumoren, die durch karzinogene Kohlenwasserstoffe erzeugt wurden, zu reproduzieren, sind nicht gelungen.

RÉSUMÉ

Dans 38 cas de tumeur maligne, les auteurs ont observé, dans les ganglions lymphatiques régionaux, des granulomes tuberculoïdes à cellules épithélioïdes. Vingt quatre de ces cas présentaient un épithélioma malpighien du col de l'utérus traité par les radiations et ont été l'objet d'examen clinique détaillé qui n'a pas mis en évidence de signes de sarcoïdose généralisée. Les auteurs décrivent le tableau histologique et concluent que les granulomes épithélioïdes dans les ganglions lymphatiques régionaux des tumeurs malignes sont une réaction sarcoïde localisée probablement due à des produits de désintégration de la tumeur. Des tentatives pour reproduire des réactions sarcoïdes dans les ganglions lymphatiques de l'oreille de lapins, par irradiation de tumeurs cutanées de l'oreille provoquées par des hydrocarbures cancérigènes, ont échoué.

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A THYROID INDEX FACTOR

by

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Various forms of the radioactive iodine tracer test of thyroid function have been used extensively during the past few years. These have proved most useful as a supplement to the measurement of basal metabolic rate (B. M. R.). However with increasing refinements, the tests have become more complex and a proper interpretation of the results may often be difficult for a physician who has no special radioisotope knowledge. (Radioactive iodine tracer test results can be presented in over twenty different ways.) Although the best diagnosis should be arrived at by a team of experts considering each problem on its merits, this is not always possible. Hence, there is a good case for presenting the clinician with a single index of thyroid function, the reliability of which he could very soon estimate for himself.

Some steps in this direction have already been suggested; *e. g.* the thyroid uptake after a standard interval of 4 hours, discussed by ANSELL et coll., or, LARSSON's quotient, 24 hour uptake divided by 24 hour urine elimination. It was decided however to investigate the possibility of deriving a simple index by making fuller use of the information available in the uptake curve.

The peak uptake. The uptake of radioiodine by the thyroid gland after a standard interval and the peak uptake have been by far the most popular measurements. Normal and abnormal levels have been described and it is generally agreed that peak thyroid uptakes of over 60 per cent of the ingested tracer dose are compatible with a diagnosis of hyperthyroidism.

Few, however, have considered the time factor involved. It is commonly observed that the time taken to reach peak uptake is related to the

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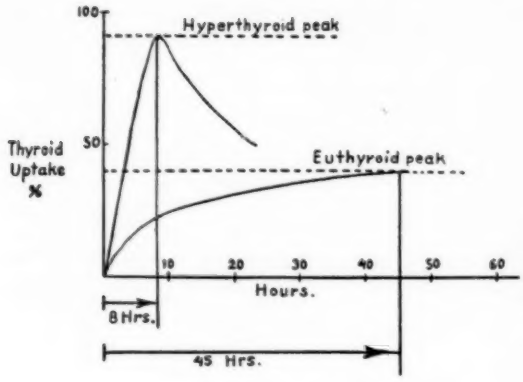

Diagram 1. Illustrating how a hyperthyroid uptake curve reaches its maximum in a shorter time than a euthyroid uptake curve — in this case, 8 hours compared with 45 hours.

magnitude of the peak. The hyperthyroid group reach their peak in a shorter time than the euthyroid group. This is because the toxic gland is quicker to drain the pool of available iodine. The time factor is seen to be important because it also reflects the avidity of the gland. Normal and hyperthyroid time factors are shown in Diagram 1.

Measurement of time factors. One hundred consecutive cases referred for radioiodine uptake tests were investigated with the time factor in mind. Only those who had had no previous thyroid therapy or no known renal disorder were chosen. The plot of peak uptake (P), against time taken to peak (T), is given in Diagram 2. It is seen that they fall about a line running from high values of P and low values of T, to low values of P and high values of T. This line intersects the euthyroid-hyperthyroid uptake borderline (taken as 52 per cent), at 39 hours on the time axis. It is suggested therefore, that for a clear radioiodine confirmation of

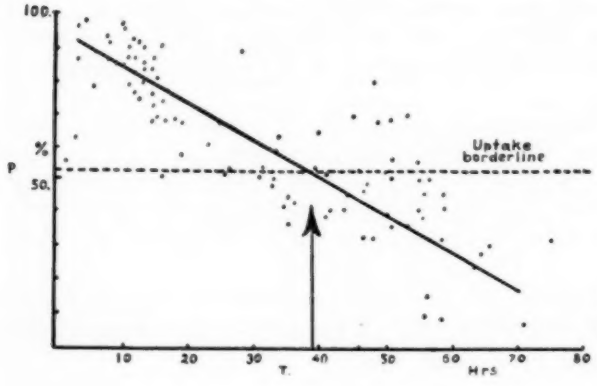

Diagram 2. Peak uptake (P) versus time taken to peak (T). 100 cases.

hyperthyroidism, the uptake curve should peak at over 52 per cent and in addition reach that peak in under 39 hours. Difficult borderline cases might profitably be reconsidered in this light.

A thyroid index. By dividing peak uptake (P), by the time taken to peak (T), we have an index factor which takes the form

$$I = A \times 1/T \times P.$$

where A equals a constant. Substituting the borderline values of P and T, we arrive at an index borderline value of

$$I = A \times 1/39 \times 52 = 1 \cdot 33 \text{ A.}$$

Choosing a suitable value of A ($A = 7 \cdot 5$), the index borderline is made equal to ten. The euthyroid index then falls roughly between one and ten, and the hyperthyroid index between ten and one hundred.

Discussion

Because thyrotoxicosis is due to excessive secretion of a normal hormone, by the very nature of things there cannot be a clear division between the normal and the toxic state. Tracer measurements confirm this continuous range of function between the two states; they further suggest that the change-over from one to the other follows either a linear or a logarithmic course. The straightforward uptake measurements lie along a linear range, but measurements — such as the protein bound iodine activity, the thyroid clearance rate, and LARSSON's quotient — which try to give a more accurate picture of the nature of things, lie along a logarithmic range (Table 1). In the slide-over from normal to pathologic the index proposed in this paper follows the latter pattern.

Table 1

Type of measurement	Non-toxic region	Toxic region	Ratio of non-toxic region to toxic region
4 Hour gland uptake % dose	0 to 40	40 to 100	1/1.5
48 Hr. P. B. plasma activity % dose/litre.....	0 to 0.4	0.4 to 4.0	1/9
Thyroid clearance rate ml/minute	0 to 80	80 to 800	1/9
The proposed index factor	0 to 10	10 to 100	1/9
LARSSON's quotient T. 24/U. 24	0 to 1.5	1.5 to 50	1/32

The more decisive logarithmic rise of the latter types of measurement is illustrated by the fraction in the final column.

Acknowledgement

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SUMMARY

From an empirical analysis of one hundred measured uptake graphs, a simple index of thyroid function has been derived. This index incorporates the peak uptake, the elapsed time between isotope ingestion and peak uptake, and a constant which has been calculated. The borderline has been so chosen that the euthyroid index lies between one and ten, and the hyperthyroid index between ten and one hundred.

ZUSAMMENFASSUNG

Aus einer empirischen Analyse von 100 Diagrammen über die gemessene Aufladung ist ein einfacher Index der Thyreoideafunktion abgeleitet worden. Dieser Index enthält die Aufnahmespitze, den Zeitverlauf zwischen der Isotopenaufnahme und der maximalen Aufladung sowie eine Konstante, die berechnet worden ist. Die Grenze ist so gewält worden, dass der euthyreoide Index zwischen 1 und 10 und der hyperthyreoide zwischen 10 und 100 liegt.

RÉSUMÉ

De l'analyse empirique de cent courbes de fixation, l'auteur a déduit un index simple de la fonction thyroïdienne. Cet index tient compte du maximum de fixation, du temps séparant l'ingestion de l'isotope du maximum de fixation, et d'une constante qui a été calculée. La limite du normal a été choisie de façon que l'index euthyroïdien varie de un à dix et que l'index d'hyperthyroïdie varie de dix à cent.

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EFFECTS OF 2-METHYL AND 2:3-DIMETHYL SYNKAVITE ON THE CHROMOSOMAL ABERRATIONS INDUCED BY FRACTIONAL AND SINGLE DOSES OF ROENTGEN RAYS

by

K. C. Bora

Studies on antimitotic and radiosensitising effects of tetrasodium dimethyl 1 : 4 naphthohydroquinone diphosphate (2-methyl synkavite) and other related compounds carried out intensively since 1947 (MITCHELL and SIMON-REUSS 1947 and 1952, MITCHELL 1949, 1950, 1951) have yielded valuable information. This work, however, has not included detailed quantitative and qualitative investigations on chromosomal effects. Although no definite correlation between cell death and chromosome damage has so far been clearly established, it is certain that major chromosome damage is a contributory factor in killing cells by ionizing radiations. Since the radiosensitising effects of the chemicals under investigation have been demonstrated, it becomes necessary to find out how and to what extent the chromosomes are sensitised by them. As MITCHELL and SIMON-REUSS (1952) suggested that the tetrasodium salt of 2 : 3 dimethyl — 1 : 4 naphthohydroquinone diphosphate (2 : 3 dimethyl synkavite), is "the most suitable compound for further investigations as a possible therapeutic radiosensitiser", this chemical has been included in the present studies.

Material and method. A Kashmir variety of broad bean, *Vicia faba*, has been used in all the experiments. Seeds were soaked in water overnight, the coats removed, and grown in test tubes for 5 to 7 days prior to irradiation of the roots. Roentgen rays were obtained from a Westinghouse machine operating at 220 kV_p and 15 mA with added filters of 1 mm Al + 0.5 mm Cu. The roots were placed at a distance of 50 cm from the source and received the dose at an intensity of 82 r per minute. Irradiations were carried

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out at room temperature and the irradiation of each series was completed on the same day and usually at the same time by putting all the beans belonging to one series in a single petri dish to exclude external variation as far as possible. Secondary roots were treated with 0.05 % colchicine for about 4 hours before fixing them in 2 BD fixative 48 hours after irradiation. Metaphase chromosomes, Feulgen stained, and squashed, were analysed for chromosomal aberrations and mitotic irregularities.

The cytologic events examined are essentially similar to those described for *Tradescantia* chromosomes (BORA 1955). Since the frequency of chromatid aberrations was found to be very low, only the chromosome breaks, interchanges, and minutes were recorded.

Experimental data. Series 1. Fractional doses. A dose of 492 r was equally divided into two halves by intervals of 3 and 6 hours (246 r + 3 or 6 hours + 246 r). The roots were treated either with distilled water, 3×10^{-4} M 2-methyl synkavite, or 2 : 3 dimethyl synkavite, during the interval. Immediately after irradiation they were washed with

Table 1

Effects of 2-methyl and 2 : 3-dimethyl synkavite on the chromosomal aberrations induced by fractional doses of 220 kV_p roentgen rays

Nature of treatment	Number of cells		Dicentric & polycentric reunions	Rings	Simple chromosome breaks	Total chromosome reunions	Total chromosome breaks	Minutes	Total chromosome breaks + minutes
	scored	damaged							
492 r	66	55	43	32	34	75	184	62	96
	69	53	43	17	21	60	141	38	59
	70	55	46	16	24	62	148	47	71
Total	205	163	132	65	79	197	473	147	226
%		79.51 ± 6.22			38.53 ± 4.33	96.09 ± 6.84	230.73 ± 10.60	71.70 ± 5.91	110.24 ± 7.33
246 r + 6 hours Water + 246 r	75	45	20	8	20	28	76	26	46
	100	55	38	12	23	50	123	39	62
	85	43	28	11	15	39	93	27	42
Total	260	143	86	31	58	117	292	92	150
%		55.00 ± 4.59			22.30 ± 2.92	45.00 ± 4.17	112.30 ± 6.57	35.38 ± 3.68	57.69 ± 4.71
246 r + 6 hours 3×10^{-4} M 2-methyl synkavite + 246 r	62	38	30	7	13	37	87	20	33
	71	48	40	12	31	52	135	35	66
	63	40	39	6	12	45	102	22	34
Total	196	126	109	25	56	134	324	77	133
%		64.28 ± 5.72			28.57 ± 3.81	68.36 ± 5.90	165.30 ± 9.18	39.28 ± 4.47	67.85 ± 5.88
246 r + 6 hours 3×10^{-4} M 2 : 3 dimethyl synkavite + 246 r	120	71	44	22	27	66	159	55	82
	120	79	51	24	24	75	174	56	80
	60	42	25	14	19	39	97	32	51
Total	300	192	120	60	70	180	430	143	213
%		64.00 ± 4.61			23.33 ± 2.78	60.00 ± 4.47	143.33 ± 6.91	47.66 ± 3.98	71.00 ± 4.86

tap water and put back in test tubes until the time of fixation. The results are shown in Table 1. It is to be noted that with an interval of 3 hours there is very little difference in the yield of chromosomal aberrations between the treatments with water and 2-methyl synkavite but with 2 : 3 dimethyl synkavite there is a considerable increase in all type of aberrations. The effect of the chemicals in increasing the chromosomal aberrations is obvious when the duration of the treatment is made longer. The difference between the two chemicals in producing chromosomal aberrations is not significant, suggesting that both may have the same potentiation value.

In experiments of this type the greater yield of chromosomal aberrations may be brought about by at least two processes: 1) It is known that most of the breaks induced by ionizing radiations either heal, take part in exchanges, or restitute within a short time of their induction (CATCHESIDE et coll. 1946, BORA 1954). The increased yield in these experiments may suggest that as a result of chemical treatment the broken ends remain open for a greater length of time. This assumption requires immediate penetration of the chemicals into the tissue. 2) The increased effect of the chemical may have been produced only by the second dose by producing more breaks due to the sensitising effect of the chemicals. How a chromosome may be made more radiosensitive is not known but there is evidence to suggest that the synthesis of DNA, the process of spiralisation, and the movement of chromosomes have been affected in the treated material.

Observations were made to ascertain whether there is any differential chemical action at different mitotic stages or specific action on the long or short chromosomes or for that matter, any other anomaly that may arise in treated cells. It is interesting to note that whereas chromatid aberrations, simple breaks and interchanges, are rare at the metaphase stage (as expected), many of the mid-prophase and prometaphase cells are with several of them. Among hundreds of metaphase cells examined not even a single cell was found with a chromatid interchange. Out of 291 mid-prophase to prometaphase cells (Table 2), eight had chromatid interchanges, present not with one or two chromatid aberrations but with many. Although these interchanges are found only in the chemically

Table 2

Effects of 2-methyl and 2 : 3 dimethyl synkavite and roentgen rays on the frequency of mitosis in the root tips of Vicia faba

Nature of treatment	Early to mid-prophase	Mid-prophase to prometaphase		Total mid-prophase to prometaphase	Metaphase	Anaphase	Total
		without chromatid interchanges	with chromatid interchanges				
246 r + 3 hours Water + 246 r.	208	87	—	87	226	63	584
Proportion	0.35			0.14	0.38	0.10	564
246 r + 3 hours 2-methyl synkavite 3×10^{-4} M + 246 r	113	173	4	177	231	43	
Proportion	0.20			0.31	0.41	0.07	
246 r + 3 hours 2 : 3 dimethyl synkavite 3×10^{-4} M + 246 r	150	110	4	114	323	17	604
Proportion	0.24			0.18	0.53	0.02	

treated cells, it is probable that they occur, perhaps with a lower frequency, in the untreated cells as well. The presence of chromatid breaks at the prometaphase stage undoubtedly suggests that these cells either belonged to a more advanced mitotic stage *i. e.* when the chromosomes were already split at the time of irradiation or the chromatid breaks were produced afterwards as a result of delayed biochemical interactions. It has been observed occasionally that some cells in a tissue are severely damaged while others do not show any visible effect at all. It is probable that the intensity of mitotic inhibition on cells belonging to a particular stage is not the same for each individual cell; some are more sensitive than others. The rate of division of cells sensitive to irradiation and possibly made more so by the chemical treatment, may have been slowed down or halted altogether at a certain developmental stage and as a consequence the radiosensitive cells appear anomalously in the tissue. It is probable that this anomaly is due to the differential action of radiation and the chemical on certain specific cells belonging to a particular stage of differentiation. An accumulation of mid-prophase to prometaphase cells suggests that 1) the early resting stage may not be uniformly sensitive to the action of the chemicals, 2) differentiating and non-differentiating cells may be affected unequally, 3) reversion, arrest, or even acceleration of mitotic speed may be taking place.

Vicia faba has two long and ten short chromosomes in the diploid complement. It could be roughly assumed that the two long chromosomes, ignoring the significance of the centromere, the secondary constriction, and the hetrochromatic region, will be equivalent in length to four short chromosomes. Table 3 shows the distribution of chromosome

Table 3

Distribution of chromosome interchanges among long and short chromosomes of Vicia faba

Nature of treatment	Number of interchanges involving		
	Long chromosomes	Short chromosomes	Total
246 r + 6 hours Water + 246 r	Observed — 44 Expected — 61	170 153	214
246 r + 6 hours 2 : 3 dimethyl synkavite	Observed — 50 Expected — 58	154 146	204

interchanges among the long and short chromosomes. The expected number has been arrived at on the assumption outlined above. There is no significant difference between the long and short chromosome as far as the frequency of interchanges are concerned, but a difference becomes apparent when the centromere, hetrochromatic region, secondary constriction, and individual length of the chromosome are brought into the picture. The presence of the centromere will probably tend to reduce the number of interchanges taking place near it due to an increase in the physical stress and strain of the proximal chromosomal segment. Unit for unit, longer chromosomes will have a smaller number of interchanges because of the greater torsional strain along the chromosome. The effect of these two factors together will be to reduce the over-all frequency of interchanges in the long chromosomes, and therefore, the frequency of interchanges per unit length of the long chromosome must be less than that of the short chromosome. On this assumption the long chromosomes are likely to be affected more than the short chromosomes.

Distribution of aberrations among. cells. While scoring the cytologic aberrations it was felt that some of the cells in the treated material had a remarkably high number of

Table 4

Percentage of cells with chromosome reunion in the root tips of Vicia faba

Nature of treatment	Number of reunions per cell				Total number of cells
	0	1	2	3	
492 r alone	39	39	17	5	205
246 r + 3 hours water + 246 r	60	29.5	7.5	3	188
246 r + 3 hours 3×10^{-4} M. 2-methyl synkavite + 246 r	60	30	9	2	196
246 r + 3 hours 3×10^{-4} M. 2:3 dimethyl synkavite + 246 r	58	24	11	7	225
246 r + 6 hours water + 246 r	71	19	7	3	260
246 r + 6 hours 3×10^{-4} M. 2-methyl synkavite + 246 r	55	33	9	3	300
246 r + 6 hours 3×10^{-4} M. 2:3 dimethyl synkavite + 246 r	52	31	14	3	196

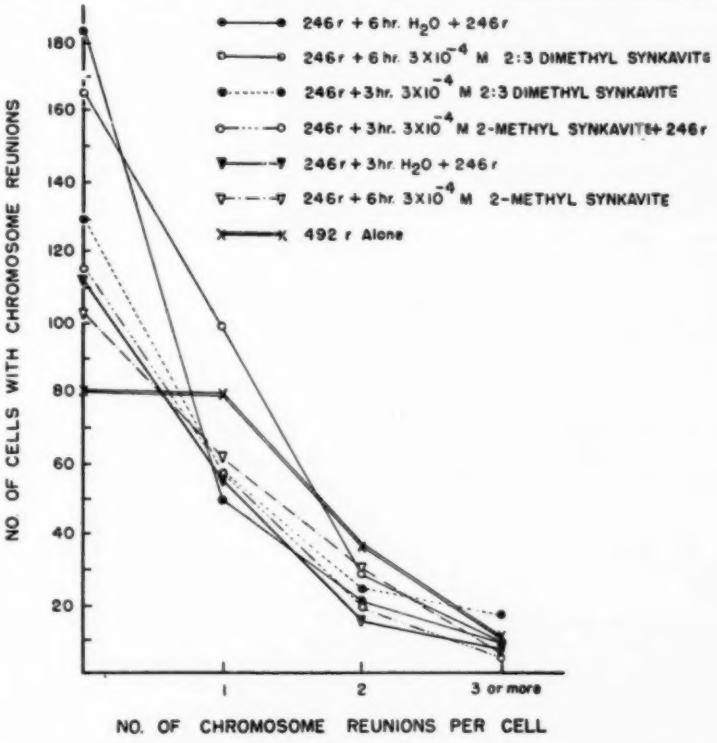

Diagram 1. Frequency distribution of cells with chromosome reunions in the root tips of *Vicia faba*.

aberrations. Indeed, in some cells the incidence of aberration frequency was so high that scoring had to be abandoned and the cells left out. A detailed study of the distribution of the aberrations among the cells was therefore made to find out whether there was any difference among the treated and control cells in the pattern of distribution. Table 4 and Diagram 1 show the percentage of cells with the number of chromosome reunions. All the treatments, except with 3×10^{-4} M 2 : 3 dimethyl synkavite for 3 hours and water for 6 hours have shown that the frequencies are distributed in the Poisson series.

Series 2. Single dose effect. Before and after treatment. The roots were treated with the compounds for 6 and 24 hours just before irradiation. In the case of the 24-hour treatment the solution was changed thrice before the time of irradiation. The roots

Table 5

Effects of 2-methyl and 2 : 3-dimethyl synkavite on the chromosomal aberrations induced by a single dose of roentgen rays

Nature of treatment	Number of cells observed	Aberrations per 100 cells					
		Damaged cells	Simple chromosome breaks	Total chromosome reunions	Total chromosome breaks	Minutes	Simple chromosome breaks + minutes
328 r alone	257	45.52±4.26	30.73±3.45	48.63±4.35	128.01±7.57	46.67±4.26	77.43±5.48
6 hours 2-methyl synkavite 3×10^{-4} M + 328 r	200	46.00±4.79	30.50±3.90	62.50±5.59	155.50±8.81	47.50±4.87	78.00±6.24
6 hours 2 : 3 dimethyl synkavite 3×10^{-4} M + 328 r	200	47.50±4.85	20.50±3.20	55.50±5.26	131.50±8.10	34.00±4.12	54.50±5.12
24 hours 2-methyl synkavite 3×10^{-4} M + 328 r	298	48.32±4.02	20.46±2.62	46.64±3.95	113.75±6.17	23.48±2.80	43.96±3.84
24 hours 2 : 3 dimethyl synkavite 3×10^{-4} M + 328 r	188	54.78±5.39	18.08±3.10	29.78±3.98	77.65±6.42	21.80±3.10	39.89±3.40

Table 6

Effects of after-treatment with 2-methyl and 2 : 3 dimethyl synkavite on the chromosomal aberrations induced by a single dose of roentgen rays

Nature of treatment	Total cells		Aberrations per cell				
	Observed	Damaged	Simple chromosome breaks	Total chromosome reunions	Total chromosome breaks	Minutes	Simple chromosome breaks + minutes
328 r alone	75	24	0.54	0.53	1.61	0.57	1.12
328 r + 24 hours 2-methyl synkavite 3×10^{-4} M	45	16	0.60	0.44	1.48	0.48	1.06
328 r + 24 hours 2 : 3 dimethyl synkavite 3×10^{-4} M	32	12	0.72	0.53	1.78	0.34	1.06

were washed in tap water prior to irradiation and fixations made 48 hours later. The results, summarised in Table 5 show an increase in the output of chromosome reunions in roots treated with either of the chemicals. It is interesting to note that the 24-hour pre-treatments have failed to produce any increase in the aberration frequency. Indeed, in contrast to other treatments, 2 : 3 dimethyl synkavite has shown significantly lower frequencies of aberrations.

The results derived from the series with after-treatment are summarised in Table 6. The low frequency of metaphase cells made it difficult to examine a sufficient number of cells. It is, however, obvious that prolonged treatment, as in the case of pre-treatment with 2 : 3 dimethyl synkavite, does not increase the aberration frequency.

Effects of the chemicals alone. MITCHELL and SIMON-REUSS (1952) claimed that various cytologic effects such as chromosome breakage etc. are produced by some of the compounds. It has also been suggested that 2 : 3 dimethyl synkavite alone is capable of producing chromosome breaks. Examination of several thousand chromosomes treated with 10^{-3} M and 10^{-4} M solutions of the compounds for various periods has not produced any evidence to suggest that these compounds alone can produce chromosome breaks in *Vicia faba* root tips. No evidence has been obtained so far to support the hypothesis of a "metabolic breakage due to the impaired synthesis of molecular structure of chromosomes".

Miscellaneous cytologic effects. There is evidence to suggest that 2-methyl synkavite may have some localized effects on chromosomes. A few cells have been observed with chromosome breaks occurring at identical loci. Fig. 1 shows two cells with similar chro-

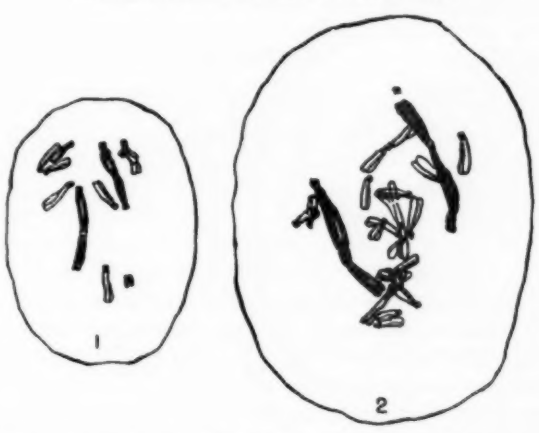

Fig. 1. Diploid and tetraploid cells showing identical chromosomal aberrations in the long chromosomes.

mosome aberrations involving long and short chromosomes. In the second cell two of the long chromosomes of the tetraploid set have been broken at identical loci. This is evident from the position of the secondary constrictions. In the first cell both long chromosomes

are affected at similar sites. It is not suggested that only the long chromosomes are affected in identical situations. The long chromosomes are easily examined due to their longer length and cytologic markers. Chromosome reunions, apparently identical and involving only the short chromosome have also been observed. More interchanges seem to occur near the centromere. From the length of the arm of the long chromosomes involved in the identical interchanges it would appear that the short chromosome is broken near the centromere whereas in the case of the long chromosome the break occurs near the distal end.

Anaphase cells in which the divided chromosomes do not move away from each other, have been observed; these chromosomes are usually longer than normal anaphase chromosomes and appear to be relatively thinner. From the arrangement of the chromosomes it appeared as if the nuclear membrane was not dissolved to allow free movement of chromosomes. These characteristics suggest that chromosomes treated with the chemicals lose capacity for movement, suggesting that the centromere has been paralysed, the chromosomes fail to spiralise, and the incorporation of DNA into the chromosome has been impaired.

The chromosomes appeared to a certain extent to be sticky. It is occasionally seen that two or more chromosomes lie in proximity in such a way that the near-ends of adjacent chromosomes seem to join together. In some cells there is a tendency for the centromeres to polarise in such a way as if a force of mutual attraction has been developed between them. In such a case all the short arms of the short chromosomes tend to lie within a small region of the nucleus.

Another point worthy of attention is the unequal speed at which the centric and the acentric chromosomes go through mitotic stages. In more than one cell it has been observed that while the centric chromosomes fully retain the morphologic characteristics of metaphase chromosomes at metaphase the acentric chromosomes are already in the process of forming micronucleus.

Discussion

The results are in general accordance with the findings of MITCHELL and SIMON-REUSS (1952). The mechanism of the radiosensitising action of the compounds must remain obscure until further data on the subject are forthcoming. Whether the chromosome loci are sensitised directly or the action on the chromosomes is of a secondary nature, probably interrupted by a series of biochemical events, must remain a speculation for the present. The detailed and specific chemical nature of *Vicia* chromosomes or for that matter of fact, any chromosome, is yet to be discovered. The breaks recovered mainly through interchanges do not seem to provide any conclusive evidence to suggest that localized chromosomal effect of the chemicals is of an intensive nature. Evidence has, however, been put forward to suggest that localized actions of the chemicals is not an improbability.

It is evident from the experimental data that the compounds alone are not capable of producing any chromosome break; nor is there any conclusive evidence to suggest that the process of rejoining and reunion is affected directly. It is, however, possible that they either enhance the breakage process initiated by ionizations or provide a favourable chemical

background for radiation action. The chemical compounds cannot affect the processes of rejoining and restitution unless the penetration of the chemicals into the cells is immediate. This would be necessary because the broken chromosome ends are usually unstable; most of them either rejoin or restitute within a short time, about 3.5 minutes (BORA 1954), after their induction. It is possible that the time required by the chemicals for entering the cells could be less than 3.5 minutes.

In experiments of this type any agent affecting the mitotic speed will modify, to a certain extent, the induced radiation effects. This may be brought about either by an accelerating mitotic speed of cells belonging to an early metabolic stage, arresting normal cells at a certain stage, for instance at metaphase, or reverting a cell belonging to an advanced mitotic stage to an early stage. It has already been mentioned that some cells show an extraordinarily high frequency of aberrations as compared to other cells of the same tissue. This would probably mean that either the radiosensitivity of these cells is much higher than the rest (perhaps genetically determined), a greater number of ionizing particles pass through them, or they belong to a more radiosensitive stage at the time of irradiation and their speed has been arrested by the treatments. It is not unlikely that in certain cases some of the so-called normal or unaffected cells actually belonged to a more radioresistant stage and their mitotic speed has been impaired to a lesser extent than cells of a more radiosensitive stage. The presence of cells with chromatid aberrations in a tissue where only chromosome breaks are expected, may serve as a proof either of reversion or arrest of mitotic speed. The non-radiosensitising affect of prolonged treatments is a matter of interest. It may be either due to the deterioration of the chemical or the production of non-radiosensitising substances.

SUMMARY

The radiosensitising effects of 2-methyl synkavite and 2 : 3 dimethyl synkavite on the chromosomes of *Vicia faba* are reported. It is suggested that both chemicals are capable of sensitising the chromosomes to radiation by an action upon a specific locus or loci. The influence of mitotic speed is discussed.

ZUSAMMENFASSUNG

Die radiosensibilisierenden Wirkungen des 2-Methylsynkavit und des 2 : 3 Dimethylsynkavit auf die Chromosomen der *Vicia faba* werden berichtet. Es wird angedeutet, dass beide Chemikalien durch Einwirkung auf einen Ort oder mehrere Stellen in der Lage sind, die Chromosomen für Strahlung zu sensibilisieren. Der Einfluss der Zellteilungsgeschwindigkeit wird besprochen.

RÉSUMÉ

L'auteur expose les effets radio-sensibilisants du 2-méthyl synkavite et du 2–3 diméthyl synkavite sur les chromosomes de *Vicia faba*. Il émet l'hypothèse que ces deux composés chimiques sont capables de sensibiliser les chromosomes aux radiations par une action sur un locus ou des loci spécifiques. Il examine l'influence de la vitesse de mitose.

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FROM THE INSTITUTE OF RADIOPHYSICS (DIRECTOR: PROF. ROLF M. SIEVERT), KING GUSTAF V JUBILEE CLINIC, KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

SCATTERED RADIATION IN A ROTATION THERAPY ROOM USING 200 KV ROENTGEN RAYS

by

K. A. Mahmoud and *K. J. Vikterlöf*

From the practical radiation protection standpoint, knowledge of the quantitative amount of scattered radiation from the patient may be of value. Investigations into this matter in diagnostic as well as in therapeutic work, using Co^{60} units, have been reported (3, 2). In conventional 200 kV treatment the geometric arrangement of the beam relative to the patient usually varies considerably, thus complicating a study of the scatter. In a rotation therapy room, however, the geometry and other factors determining the scatter are fairly constant, which greatly facilitates the investigation and makes it possible to study the pure scatter.

The rotation therapy equipment at Radiumhemmet was considered suitable, and hence used, for such a study. This equipment is designed especially for precision treatment of intrathoracic lesions (1). The walls, floor, and ceiling of the rotation therapy room have protecting barriers equivalent to 4 mm of lead, a value which rises to 6 mm lead for the observation window, struck by the direct beam. The maximum dose measured per week outside the room is 20 mr, referable to about two hours irradiation daily.

These barriers inevitably scatter radiation back into the room, and this is added to the scattered radiation from the patient and the machine with its installations. Hence it is important, from the protection point of view, to estimate the distribution of these scattered roentgen doses in the rotation therapy room. This paper is concerned with some of the isodose patterns of the scattered radiation in space inside the room under ordinary clinical conditions.

Scattering material. As a scattering medium we used physically correct anatomic phantoms constructed by one of us (VIKTERLÖF) and Dr.

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DAHL at Radiumhemmet, but not yet published. The phantoms are so designed that: 1) bone is taken from human skeletons, boiled in vacuo in paraffin; 2) all soft tissues except lungs are made of a water-equivalent material Mix D (5); and 3) lungs are composed of sawdust (density 0.2 g/cm³), as developed in an investigation by DAHL and VIKTERLÖF (4); to be published in greater detail later on.

We have used two thorax phantoms of sizes representing patients of different dimensions in different treatment positions.

Radiation measuring system. Measurements were made with the double ionization chambers described by SIEVERT and WALSTAM (6). These chambers were found to be convenient for these measurements, since they had an extensive measuring range, and because of their wide directional and quality independence, the latter ranging from the soft diagnostic up to the conventional deep therapy range. The chambers were charged and read by an instrument designed by SIEVERT (7). This instrument proved to be satisfactory for our purpose and our experimental conditions.

It was important for us to have the chambers calibrated in order to recheck their quality independence. For that reason, all the 22 chambers used in the measurements were calibrated against a substandard high sensitivity chamber unit, number 204, designed by THORAEUS (8). This unit has a sensitivity defined by the average k value of 2.55×10^{-5} r per volt, $\pm$ 3.5 % in the wide range from 400 kV half-wave tube voltage, 7 mm Pb additional filter, and using a tube having an inherent filtration equivalent to 0.6 mm Cu, down to 40 kV constant potential tube voltage, no additional filter, and using a tube having an inherent filtration equivalent to 0.95 mm Al.

The Sievert chambers were calibrated at a free-air focal distance of 5.8 metres in the standard laboratory of this institute, in cooperation with THORAEUS, who made available both the substandard mentioned and the equipment of that laboratory.

The quality independence of the chambers was checked in the range between 200 kV constant potential with an additional filter of 0.2 mm Cu + 1 mm Al, and 93 kV constant potential with an additional filter of 1 mm Al, using a tube with an inherent filtration equivalent to 1.5 mm Al. This range was still within the wide range of the substandard high sensitivity chamber and proved to be good enough for our isodose measurement quality calibration. The calibration results for each of the chambers were found to be practically the same within an accuracy limit of $\pm$ 6 per cent.

Experimental. Fig. 1 shows the geometric arrangement of the tube, the phantom on the rotation chair, the fluoroscopic screen unit with its suspension devices as well as the chamber used for transit dose meas-

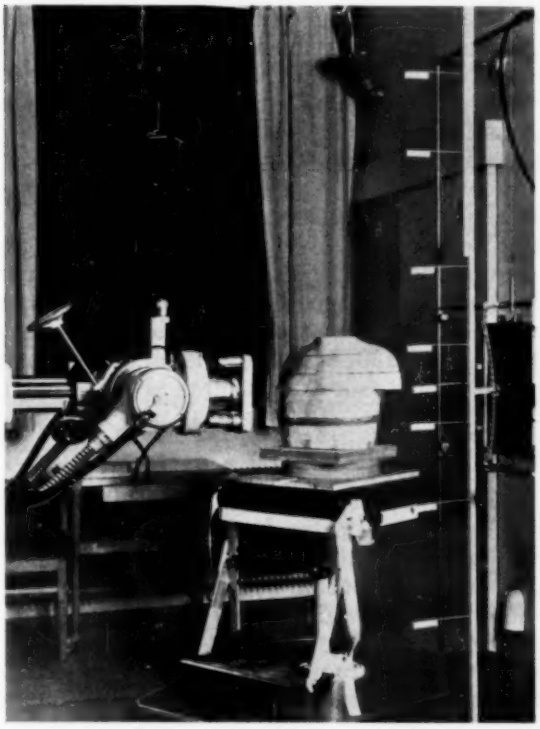

Fig. 1. Geometric arrangement of experimental set-up.

urement in the treatment room. The chamber is connected to the Philips integral dosimeter in the control room. The detectors can be seen to the right and consisted of Sievert ionization chambers, mounted on thin wooden sticks 2 mm in diameter and 15 cm in length. These sticks can easily be mounted in and removed from fixed holes in a vertical wooden stand. The dimensions of this stand, 2 cm in thickness and 3 metres in height, were sufficient to preclude any influence on the dose measurement due to its own scattering. This was confirmed by a preliminary experiment in which the chambers were suspended by means of thin thread. Since no significant variation was found in the measuring values, it was decided to use the wooden stand for practical convenience. The floor and ceiling of the treatment room were ruled with identical co-ordinate systems to facilitate adjustment of the wooden stand to any desired position in the area.

The phantom on the rotation chair and the equipment were arranged

as in treatment of a patient with carcinoma of the oesophagus. The rotation therapy machine was thus operated at a tube voltage of 200 kV constant potential, with an additional filter of 0.2 mm Cu + 1 mm Al which gave a H. V. L. of 0.7 mm Cu. The focus axis distance was adjusted to 60 cm. The radiation output was kept extremely constant by means of the monitoring filter designed by THORAEUS (9). The field sizes used had the dimensions of 4 × 10 cm, 6 × 15 cm and 10 × 20 cm, geometrically referable to the rotation axis. The rate of rotation of the phantom was 36 seconds per revolution. All measurements were taken over a whole number of revolutions. The transit dose chamber was used as a secondary monitor throughout the whole measurements.

The Sievert chambers were mounted on the vertical stand at heights of 20, 60, 110, 120, 130, 150, 180, 220, 260, and 300 cm from the floor. The central line of the roentgen beam was always kept at a height of 120 cm. The measurements were repeated with the stand in different positions in the rotation therapy room. This positioning followed a polar displacement, *i. e.*, different horizontal positioning for different polar lines. The measurements were made only for one half of the treatment room; the other half was considered to be symmetric.

Comparative measurements were made with the larger phantom, using the biggest field size, but no significant difference was found. This means that the isodose curves given are applicable to all patients without any significant error.

Results and discussion. From the uniformly monitored measurements using the smaller phantom, we were able to express our results in terms of mr per min at a constant transit dose value and to give our data in the form of isodose patterns for eleven horizontal levels for each of the three field sizes used in our investigations. The isodose values were expressed as percentages of the air dose at the rotation axis with a drawing accuracy of ± 10 per cent. The shape and percentage of the isodose curves were found to vary slightly with the field size. We have therefore presented only the isodose curves measured with 10 × 20 cm and 4 × 10 cm field size (Figs. 2 and 3).

From Fig. 2 it will be seen that for the 10 × 20 cm field the percentage dose increased, starting from the lowest horizontal level (20 cm above the floor) and upwards to the 120 cm level which passed through the central line of the roentgen beam. The isodose curves then started inversely to repeat themselves, with slight variations. For example, the 110 cm height isodose curves are nearly the same as those at 130 cm, and so on for the 90 and 150, 60 and 180, and 20 and 220 cm heights respectively. Existing small variations may be attributable to particular selective absorption in and scattering from some parts of the equipment. It will also be seen that all the isodose curves tend to show a maxi-

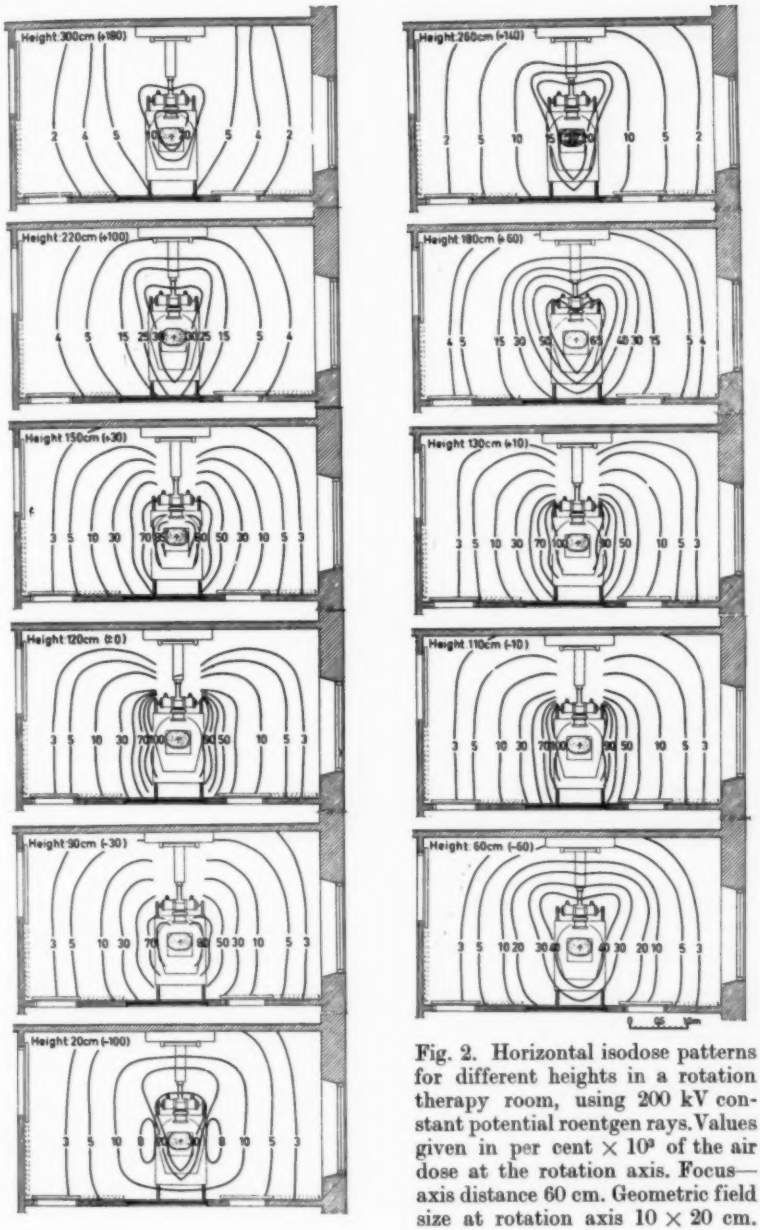

Fig. 2. Horizontal isodose patterns for different heights in a rotation therapy room, using 200 kV constant potential roentgen rays. Values given in per cent $\times 10^2$ of the air dose at the rotation axis. Focus—axis distance 60 cm. Geometric field size at rotation axis 10 × 20 cm.

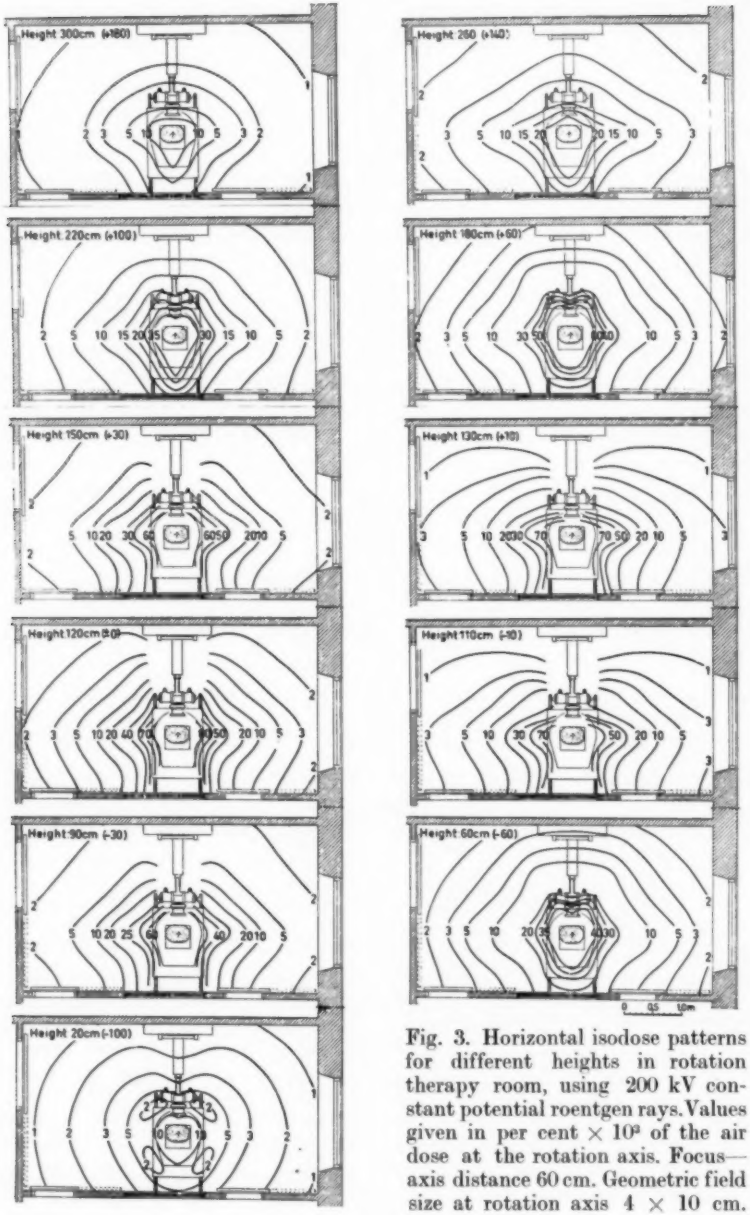

Fig. 3. Horizontal isodose patterns for different heights in rotation therapy room, using 200 kV constant potential roentgen rays. Values given in per cent $\times 10^2$ of the air dose at the rotation axis. Focus—axis distance 60 cm. Geometric field size at rotation axis 4 $\times$ 10 cm.

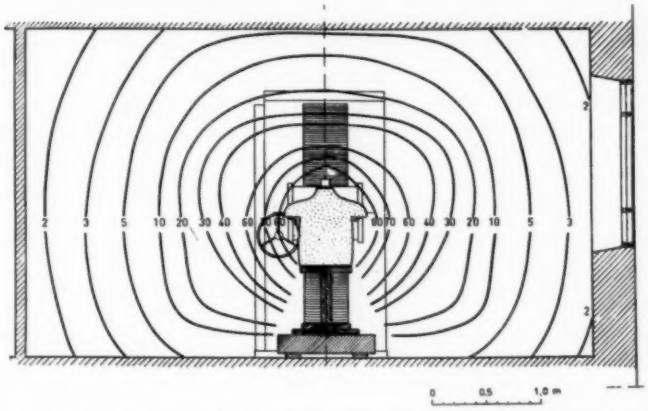

Fig. 4. Vertical isodose pattern in a plane passing through rotation axis perpendicular to roentgen ray beam. Experimental conditions as in Fig. 2.

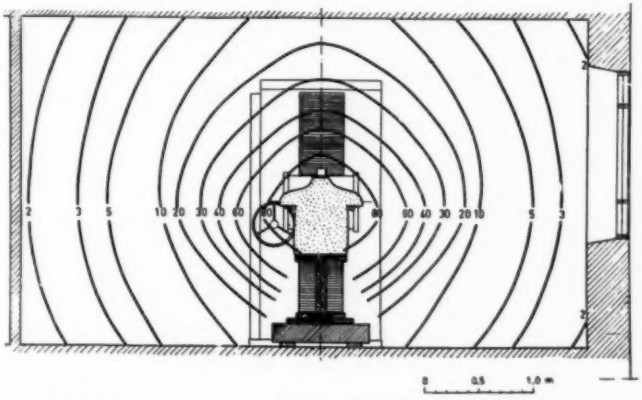

Fig. 5. Vertical isodose pattern in a plane passing through rotation axis perpendicular to roentgen ray beam. Experimental conditions as in Fig. 3.

mum value at an average angle at 150° from the horizontal beam direction. This is caused by a narrow leakage of secondary radiation at the opening for the monitoring filter. This leakage is small in comparison with the primary central axis dose rate, but it is a major factor in comparison with the scattered radiation.

On comparison of the isodose curves for the 10 × 20 cm field size (Fig. 2) with those for the 4 × 10 cm field size (Fig. 3), the most striking feature is the decreasing amount of back-scattered radiation. Further-

more, there is also another tendency to a maximum at an average angle of 90° from the beam direction. This may be caused by diffracted and reflected radiation from the small-area applicator (2 × 5 cm), and by leakage radiation from the tube container. The variation in the percentage isodose curve is quite small, even with the comparatively large differences in field size. For both fields the isodose curves have a long tail towards the zero angle which is mainly due to the increasing direct radiation interference. This interference is more pronounced near the central horizontal plane. For that reason it was necessary to break the isodose curves at an opening angle of 60°.

In order to obtain a better three-dimensional isodose picture of the scattered radiation, the isodose curves in the vertical plane should be given. For this purpose we have chosen the vertical isodose pattern which represents the distribution in the plane passing through the rotation axis perpendicular to the roentgen ray beam. These isodose curves for the two field sizes are shown in Figs. 4 and 5. Minor variations will be observed in the shape and percentage of the isodoses.

Lastly, the distribution shown in Figs. 2, 3, 4 and 5 represents the scattered radiation from the phantom, the walls, ceiling, and floor, as well as from the machine in a rotation therapy room, using 200 kV roentgen rays. The distribution found is practically independent of the field size used.

SUMMARY

A three-dimensional isodose picture of the scattered radiation in the 200 kV roentgen ray rotation therapy room at Radiumhemmet, is given in the form of horizontal and vertical isodose curves. It was found that the distribution of the isodose curves is practically independent of the size of the patient and the range of field sizes used.

ZUSAMMENFASSUNG

Die dreidimensionale Dosisverteilung der Streustrahlung im 200 kV Rotationsbestrahlungszimmer des Radiumhemmet wird in Form von horisontalen und vertikalen Isodosen vorgelegt. Die Dosisverteilung wurde von den Patientdimensionen und den angewandten Feldgrössen nur unerheblich beeinflusst.

RÉSUMÉ

Les auteurs donnent, sous forme de courbes isodoses horizontales et verticales, une représentation tridimensionnelle des isodoses du rayonnement diffusé dans la salle de roentgenthérapie rotatoire à 200 kV du Radiumhemmet. La distribution des courbes isodoses est pratiquement indépendante de la taille du malade et de la dimension des champs utilisés.

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BOOK REVIEW

STUDIES ON THE DISTRIBUTION OF TRITIUM-LABELLED DIHYDROSTREPTOMYCIN AND TETRACYCLINE IN THE BODY. By TORSTEN ANDRÉ. 89 pp, 41 illustrations, 1 table. Acta radiol. Suppl. 142 (1956). Sw. Kr. 25: —.

The aim of this investigation was to study some of the pharmacologic properties of dihydrostreptomycin and tetracycline, how they are distributed by the blood to different body tissues, how they are excreted and if they are inactivated in the body. For an antibiotic to exert its antibacterial activity in the body it must come in contact with the pathogenic microbes and its concentration in the immediate vicinity of these must be sufficiently high. A careful study of the distribution pattern in both normal and pathologically changed tissues is therefore of therapeutic interest.

By synthesis on a microscale dihydrostreptomycin and tetracycline containing radioactive hydrogen, tritium (H^3), have been prepared and their distribution has been studied with an autoradiographic technique.

The synthesis of radioactive dihydrostreptomycin and tetracycline is described. Exchange reactions, the use of various isotopes, and their advantages and drawbacks are discussed. Analyses and radioactivity determinations are outlined. The technique was adapted to the requirements imposed by the water solubility of dihydrostreptomycin and tetracycline and also to the desire to obtain full-section autoradiograms, *e. g.*, of whole mice. A partly new technique was also elaborated for localization at the cellular level in which small, thin sections, dried by freezing, were brought into permanent contact with the autoradiographic emulsion.

The preparation of a tritium standard for densitometric determinations is reported, together with the effects on the film emulsion of variations in temperature of the developer, and in development time and exposure time. The quantitative evaluation of the autoradiograms with the aid of densitometric readings is set forth.

Full-section autoradiograms illustrating the distribution of dihydrostreptomycin and tetracycline in adult mice at different times after intravenous injection are given. Large full-section autoradiograms of pregnant animals permitted studies of tracer distribution in the foetus and foetal fluids in the same film as the mother.

Films are shown illustrating the detailed distribution of dihydrostreptomycin and tetracycline in regions of special clinical interest such as the brain, eye, sinuses of the skull, nasal conchae, teeth and paradental tissue, synovial cavities, skin, and bone-marrow.

The localization of the investigated antibiotics on the cellular level is also illustrated.

The investigations also provided possibilities of studying the different paths of excretion as well as the problem of accumulation in the organs. Observations were made on the penetration of dihydrostreptomycin and tetracycline into abscesses. Both antibiotics passed through the abscess membranes and were also present in lower concentration throughout the abscess content.

The stability of dihydrostreptomycin and tetracycline during their passage through the body was investigated. Radioactive dihydrostreptomycin and tetracycline were injected into mice and the urine from the experimental animals was examined by means of paper chromatography. The urine, it was found, did not contain radioactive substances other than the relevant antibiotics. From this observation it was inferred that the antibiotics were not broken down to any appreciable degree in the body during the five hours covered by the experiment.

Autoreview.